A FEASIBILITY STUDY FOR THE REPORTING OF CERVICAL LARGE LOOP EXCISIONS OF THE TRANSFORMATION ZONE (LLETZ) BIOPSIES BY CONSULTANT BIOMEDICAL SCIENTISTS IN THE UK

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Abstract

Objective – A previous pilot study had shown that there was potential to extend the roles of advanced biomedical scientist practitioner (ABMSPs) now referred to as Consultant Biomedical Scientists (BMS) to report the histology of large loop excision biopsies of the cervical transformation zone (LLETZ) within the NHS Cervical Screening Programme (NHSCSP).

Methods - 157 consecutive LLETZ specimens reported by four experienced Gynae-specialist Consultant Histopathologists at Sheffield Teaching Hospitals NHS Foundation Trust, were also reported by six Consultant BMS, and compared against the final issued report. Neoplastic abnormalities were reported to NHSCSP standards as well as the Bethesda system. Completeness of excision and histological features associated with the presence of human papillomavirus (HPV) infection were also assessed. The reporting of HPV is part of the proforma for reporting cervical samples, it does not affect the patient management but allows for correlation with the cervical cytology report and hence was included as part of the study.

Results - There was overall good inter-observer agreement for both the three tier and two tier system of grading squamous lesions plus good agreement for glandular and invasive carcinomas identified by the Consultant BMS. There was variable inter-observer agreement for the

completeness of the excision of the margins and the presence of HPV.

Conclusions - This report provides evidence that suitably experienced Consultant BMS can be 'fast-tracked' through an approved training programme of selected specimens to meet the needs of the Histopathology service that is facing a chronic shortage of Histopathologists in a timely manner and provide a cost-effective solution.

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Introduction

Over the last couple of decades, roles that were traditionally undertaken by the medical profession have been transferred to appropriately trained non-medically qualified practitioners in the National Health Service (NHS). These roles have rapidly expanded in many areas of healthcare, notably nursing and diagnostic imaging (Sibbald et al, 2006). In the field of radiography, radiographers who used to be known as x-ray technicians have taken on advanced practitioner roles that were traditionally undertaken by medical radiologists such as administering intravenous injections, barium enemas and reporting images e.g. mammography images (Price and Le Masurier, 2007: Nightingale and Hogg, 2003). Advanced nurse practitioners (ANP) have been shown to be an important step in the pathway of patient care by assessing whether they need to see a doctor or can be treated by an ANP or another health professional. The following definition of an ANP could also be applied and adapted to the role of the Consultant Biomedical Scientist (BMS) in cervical cytology and defines the ANP as "an advanced level clinical nurse who through extra education and training is able to practice autonomously, making clinical decisions and instigating treatment decisions based on those decisions, and is fully accountable for her own practice" (Royal College of Nursing, 1989).

The Consultant BMS in cervical cytology has undergone extra training and is competent to practice independently once they

have passed their final exit examination – the Advanced Specialist Diploma in Cervical Cytology.

Advanced roles in Healthcare Science

The first advanced role in healthcare science was the advanced biomedical scientist practitioner (ABMSP) in cervical cytology now known as Consultant Biomedical Scientists (BMS). Consultant BMS in cervical cytology were first introduced in the year 2000 due to a chronic shortage of Consultant Histopathologists specialising in cervical cytology and quality concerns that were raised by incidents in the cervical screening programme in Kent and Canterbury (Prichard, 1996: Johnson and Patnick, 2000). Consultant BMS were introduced to the NHS Cervical Screening Programme (NHSCSP) following acceptance by the Department of Health to a joint proposal from the Royal College of Pathologists (RCPath) and the Institute of Biomedical Science (IBMS) (The Royal College of Pathologists, 2000) and in line with 'Making the Change – A Strategy for the Professions in Healthcare Science' (Department of Health, 2001).

The aim of this joint proposal was to extend the practice of senior experienced BMS to report abnormal cervical cytology samples and recommend patient management such as referral for colposcopy and early repeat of testing. The Consultant BMS have the knowledge and experience to offer clinical advice to sample takers and to provide help/support for the cervical screening team in their laboratory. In some hospitals,

Consultant BMS are expected to provide cervical cytology training for the junior medical pathologists, as well as training for non-medical staff. They would also be expected to present their cases to the Colposcopy multidisciplinary team (MDT) meetings where any discrepant or mismatch cases would be discussed between the Colposcopy clinician, Histopathologists and Cytologists to determine the best way forward for the woman, whether that is further treatment, surveillance or discharge back to primary care. As can be seen from the above, the new role of the Consultant BMS has an extensive role and is equivalent to a medically qualified pathologist but only in the area of cervical cytology.

Recent best practice recommendations from the Royal College of Pathologists, has stated that Consultant BMS can be the clinical lead for the cervical screening service. The clinical lead is defined as the individual 'who takes overall responsibility for the clinical quality and governance of a service.' Although everybody within the cervical screening department is responsible for ensuring quality and governance, the clinical lead as the name suggests has the ultimate responsibility for leading and giving direction (The Royal College of Pathologists, 2019).

Eligibility criteria and the training programme for BMS has modified over the years since the onset of the original examination in 2000 as the qualification has matured (Smith and Hewer, 2003: Symonds, 2003: Institute of Biomedical Science, 2018).

Suitable candidates must be state-registered with the Health and Care Professionals Council (HCPC) as a biomedical scientist, have at least seven years of primary cytology screening experience post NHSCSP Certificate of Competence or equivalent, be a Fellow or Member of the Institute of Biomedical Sciences (IBMS), have a minimum of three years as a 'checker' plus service management and a statement from the clinical lead supporting the candidate. These candidates will undergo an approved training programme under the supervision of a Consultant pathologist practising cervical cytology. On completion of their training portfolio, they have to pass the examination for the Certificate in Advanced Practice, now known as the Advanced Specialist Diploma (ASD) in Cervical Cytology, managed by the Conjoint Board of the RCPath and IBMS before they can be appointed to the reporting position of a Consultant BMS. Since the start of the examination there have been more than 100 successful candidates with an overall pass rate of 57.5% (Wilson, 2019).

There are a number of extended and advanced roles within healthcare science and pathology in the UK that were traditionally performed by medically qualified pathologists that are now undertaken by biomedical scientists. These have followed on from the successful introduction of the Consultant BMS in cervical cytology employed by laboratories providing screening for the NHSCSP. For suitably experienced BMS there are four more ASDs available in Ophthalmic Pathology, Specimen Dissection, Non-Gynaecological Cytology and

Histopathology Reporting (Institute of Biomedical Science, 2019). These changes have been driven partly by pathology reviews and workforce reviews to address the national shortage of pathologists (Department of Health, 2004).

Following on from the successful introduction of the Consultant BMS in cervical screening departments in the UK, other countries are looking to introduce advanced roles for their scientific staff most notably the cytotechnologist pathologist extender in the USA (Sweeney and Wilbur, 2018). As the discipline of cervical cytology is changing world wide, alternative role are being developed for cytotechnologists such as the prescreening evaluation of fine needle aspirates (FNAs) and rapid on site evaluation (ROSE) of the adequacy of samples taken in clinics and microscopy interpretation of fluorescence in situ hybridization (FISH) (Cahill, 2014: Gonzalez et al, 2017).

There are currently approximately 55 Consultant BMS in cervical screening with reporting roles in the UK and this number will reduce with their microscopic skills lost to the service as the changes continue with the way the NHSCSP delivers cervical screening. The workloads in cervical screening services have reduced due to changes in NHS screening policies such as the introduction of liquid based cytology (LBC), Human Papillomavirus (HPV) testing and automation plus the onset of the HPV vaccinated cohort (National Institute for Health and Clinical Excellence (NICE), 2003: Moss et al, 2004: Arbyn et al, 2005: Kitchener et al,

2009: Ronco et al, 2010: Murphy et al, 2012: Cuzik et al, 2010). As the vaccinated cohort enters the cervical screening programme there will be further reductions in cervical disease (Kohli et al, 2007) and this has already been seen in the Scottish cervical screening programme (Palmer et al, 2019). This is further compounded by reductions in screening workloads due to the consolidation of laboratories from 46 to eight centres nationally with the introduction of HPV primary screening.

As the scope for the Consultant BMS in cervical cytology is changing, in the background, pathology services are facing a chronic shortage of Histopathologists. There are many vacancies for Consultant Histopathologists locally and this was corroborated in a survey by the Royal College of Pathologists in September 2018. The survey confirmed that only 3% of histopathology departments have enough staff to meet the demands of their clinical service and approximately 25% of the workforce is over the age of 55 due to retire in the near future (Royal College of Pathologists, 2018). Histopathologists are vital in the role of diagnosing diseases such as cancer and giving guidance to the clinician as to the best treatment pathways for their patients. These shortages could contribute to delays in patient diagnosis and management. A plan is in place to introduce new Histopathologists but this will take time, however by utilising the skills of Consultant BMS in selected areas such as cervical pathology, this should allow Histopathologists to concentrate on the more complex areas of

their workload in the interim period and should be more cost-effective. As stated earlier, there have been developments in extended roles for experienced BMS such as specimen dissection and non-gynaecological cytology. The help of the BMS in these extended roles has been met favourably by Histopathologists and have helped with their management of their workloads (Duthie et al, 2004: Simmons et al, 2011).

It is important to understand the NHSCSP and how Consultant BMS have contributed to the success of the programme with their skills and specialised knowledge. Consultant BMS have proved their extensive knowledge of cervical disease and the NHSCSP with the exit examination of the Advanced Specialist Diploma in cervical cytology. As described earlier, the delivery of the NHSCSP has changed and will continue to develop with a loss of these highly motivated and specialist staff unless alternative roles can be found that will utilise their skills and knowledge. The basis of this study is to evaluate how the skills of the Consultant BMS can be utilised further.

NHS Cervical Screening Programme (NHSCSP)

Screening Programmes

A medical screening programme tests the asymptomatic population for a disease that is a precursor of cancer such as the breast and cervical screening programmes. The conditions for a successful screening programme for the World Health Organisation (WHO) were set by Wilson and Junger (Wilson and Junger, 1968). A disease which is suitable for screening as identified by Wilson and Junger should meet the following ten conditions

1. *The condition sought should be an important health problem*
2. *There should be an accepted treatment for patients with recognised disease*
3. *Facilities for diagnosis and treatment should be available*
4. *There should be a recognisable latent or early symptomatic stage*
5. *There should be a suitable test or examination*
6. *The test should be acceptable to the population*
7. *The natural history of the condition, including development from latent to declared disease, should be adequately understood*
8. *There should be an agreed policy on whom to treat as patients*
9. *The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole*

10. *Case-finding should be a continuing process and not a "once and for all" project*

The principles for screening have been updated to take in to account of recent screening developments (Andermann et al, 2008)

- *The screening programme should respond to a recognised need*
- *The objective of screening should be identified at the outset*
- *There should be a defined target population*
- *There should be scientific evidence of screening programme effectiveness*
- *The programme should integrate education, testing, clinical services and programme management*
- *There should be quality assurance, with mechanisms to minimise potential risks of screening*
- *The programme should ensure informed choice, confidentiality and respect for autonomy*
- *The programme should promote equity and access to screening for the entire target population*
- *Programme evaluation should be planned from the outset*
- *The overall benefits of screening should outweigh the harm*

Screening to prevent cervical cancer follows the above principles for a screening programme as cervical intraepithelial neoplasia (CIN) is the recognised precursor stage for cervical cancer which can be identified with cervical cytology.

As we continue to understand how cervical cancer develops, it has been recognised that women have to be exposed to 'high risk' HPV by skin-to-skin contact and once integrated in to the DNA of cervical cells causes over 99% of cervical cancers (Walboomers et al, 1999: Bosch et al, 2002). Over 80% of women will come into contact with HPV, however most of them will clear the infection within two years. Some women are unable to clear the HPV infection, known as persistence and together with other factors such as immunodeficiency, smoking and sexual activity are at higher risk of developing cervical cancer (Burd, 2003). Cervical cancer can take up to 20 years to develop from the first exposure to HPV developing in to CIN and becoming invasive (Sherris et al, 2001).

Cervical screening can detect these early stages of cervical cancer by using HPV testing and cytology. This allows the woman to be diagnosed and treated before the disease which if left untreated may go on to develop in to cervical cancer (Denny, 2008). We do not know which women who get diagnosed with cervical precancer will go on to develop cervical cancer, hence we have to treat them as the worst case scenario (McCredie et al, 2008).

The cervical screening test on the whole is seen as an acceptable test following the WHO guidelines as it is a minimally invasive procedure and the sample can be taken in primary care. Some women may disagree with this statement as they find attending for cervical screening embarrassing and some of them may find it to be an uncomfortable procedure (Waller et al, 2009). These are just some examples of the barriers that are putting women off for attending cervical screening resulting in low coverage. Coverage in 2013-14 was

74% and in 2016-17 was 72 % below the lower threshold of 75% and well below the national target of 80% (Department of Health & Social Care, 2019). The trend of coverage dropping continued in 2017-18 with the coverage rate at 71.4% (NHS Digital, 2018).

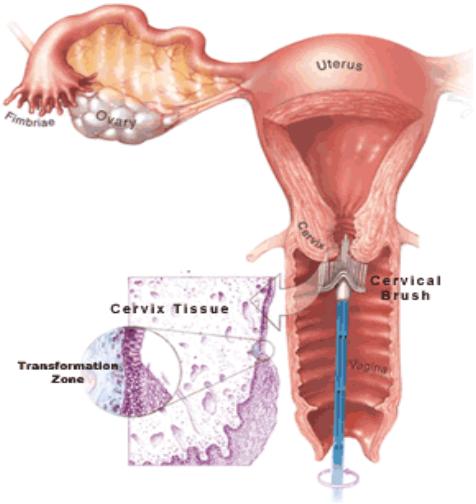
'The primary aim of the NHSCSP is to reduce both the incidence and mortality from cervical cancer by regularly screening all women so that conditions which might otherwise develop into invasive cervical cancer can be identified and treated at an early stage with a better prognosis. Currently women are invited from the age of 25 to 49 years of age every three years and from 50 to 64 every five years to attend for cervical screening' (Public Health England, 2015).

The NHSCSP has been very successful since it was formally introduced in 1988 and it has been estimated that the NHSCSP has saved 4,800 women per year from dying of cervical cancer in the UK (Peto et al, 2004).

Cervical Screening Test

In England, women are invited to attend for cervical screening every three to five years where a sample is taken from the cervix at the area where the epithelium changes from the multi-layered ectocervical epithelium to the monolayer endocervical epithelium known as the transformation zone. The transformation zone is represented in Figure 1 and in the histological section of the cervix in Figure 2

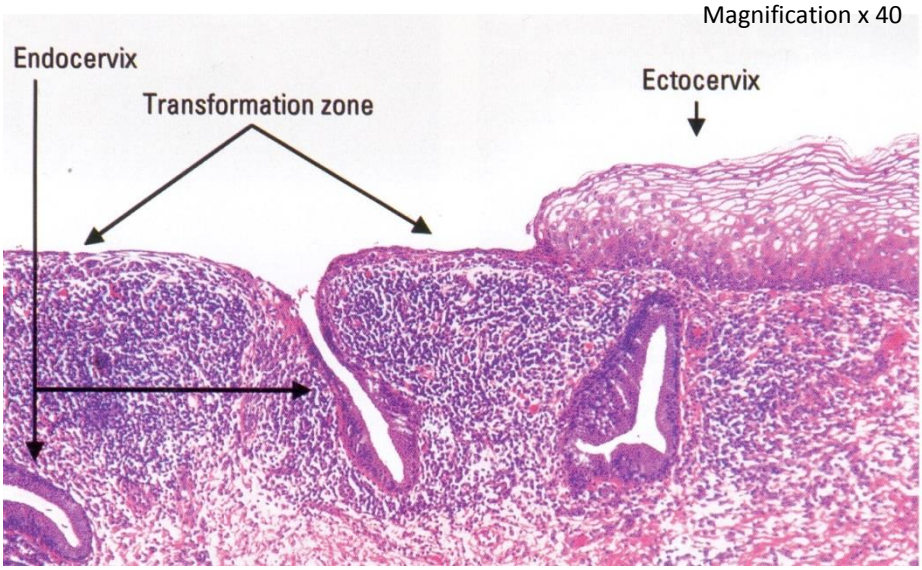
Figure 1 Diagram of uterus and cervix to demonstrate sampling area



Courtesy of Johns Hopkins Medicine

Figure 2 Histological representation of epithelium of the cervix

Magnification x 40



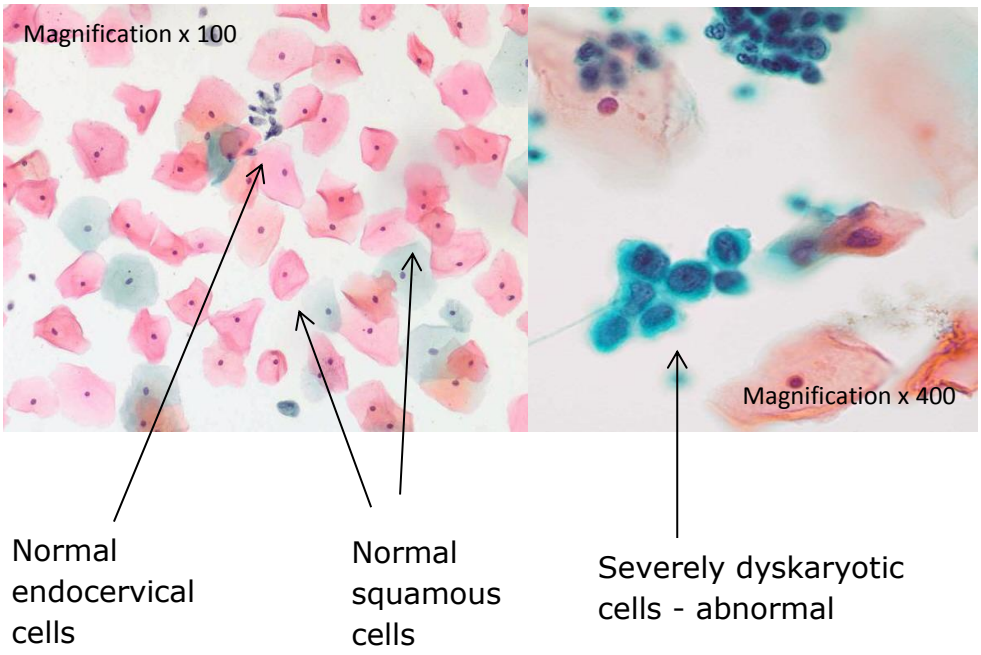
Slide from own collection

When the NHSCSP first commenced, cells were directly smeared on to a glass slide and fixed. The slides were then

sent to the laboratory for staining and microscopic examination. This is where the term 'cervical smear' originates from. The 'cervical smear' or 'Pap test' remained the same for over 50 years before new technology was introduced. Once the slide is produced by whatever technique, the method of evaluation is fundamentally the same. A cytologist looks down the microscope to critically evaluate the cells looking for changes which may indicate a cervical abnormality that needs further investigation (Figure 3).

Normal and abnormal cells from the cervix were first described and drawn by George Papanicolaou who devised the term dyskaryosis (Papanicolaou and Traut, 1941: Papanicolaou, 1963). Dyskaryosis is derived from 'dysk' which is Greek for abnormal and 'karyon' is Greek for nut or nucleus. In the UK, dyskaryosis is used to describe and grade the abnormality of cells from cervix (Denton et al, 2008). The different cytology grades are listed in Table 1 with their corresponding histological grades of CIN, cervical glandular intraepithelial neoplasia (CGIN) and cancer. In the rest of the world different terminology is used most notably The Bethesda System is used in the USA and extensively in Europe (Solomon, 2002: Nayar and Wilbur, 2014).

Figure 3 Images of normal and dyskaryotic cells



Slides from own collection

New techniques are always evaluated by the NHSCSP prior to introduction to the programme to ensure that they are as least as good as previous methods and are cost-effective. Liquid based cytology (LBC) was a new technology and was introduced in to the NHSCSP on 2003 following the recommendation of the National Institute for Health and Clinical Excellence (NICE, 2003) plus the results of the pilot study (Moss et al, 2006).

Table 1 UK cytology terminology with corresponding histology terminology

Previous terminology (BSCC 1986)	New terminology (BSCC 2008)	Histopathology terminology
Inadequate	Inadequate	N/A
Negative	Negative	No CIN/ HPV changes only
Borderline change	Borderline change in squamous cells	Corresponds to low grade CIN
	Borderline change in endocervical cells	Possible low grade CGIN (classified as high grade histology)
Mild dyskaryosis	Low-grade dyskaryosis	CIN 1
Borderline change with koilocytosis		
Moderate dyskaryosis	High-grade dyskaryosis (moderate)	CIN 2
Severe dyskaryosis	High-grade dyskaryosis (severe)	CIN 3
Severe dyskaryosis, possibly invasive	High-grade dyskaryosis/possible invasive squamous carcinoma	Squamous cell carcinoma
? Glandular neoplasia*	? Glandular neoplasia of endocervical type*	CGIN
	? Glandular neoplasia (non-cervical)*	Non-cervical cancers e.g. endometrial

* ? as expressed in front of glandular neoplasia is recognised terminology used by the NHSCSP suggesting that the lesion maybe derived from the glandular epithelium of the cervix

however it is not conclusive and may be from other parts of the female genital tract.

Liquid based cytology (LBC)

LBC is a technique where cells that have been sampled directly from the cervix are placed in a vial composed of alcohol with a blood-lysing agent. The exact composition of the medium is protected by the trade names of ThinPrep® or SurePath™. The vials are sent to the laboratory for processing on the ThinPrep® or SurePath™ platforms. LBC lets the laboratory control the processing improving the quality of the sample ensuring that the final preparation is uniform, cleaner and a smaller area to screen (Moss et al, 2006). There are many advantages to using LBC such as the preparations are cleaner and quicker to screen with a reduction of inadequate rates from 9% to 1.6% (National Institute for Health and Clinical Excellence (NICE), 2003: Gupta et al, 2016). As there is residual material within the vial extra preparations can be made for teaching purposes and adjunctive tests can also be performed. Adjunctive tests include HPV testing and molecular markers such as CINtec® *Plus*Cytology. CINtec® *Plus*Cytology is a dual-biomarker that has a strong association with high grade cervical disease as p16 is a surrogate marker for HPV infection and Ki67 is a marker for cell proliferation (Wright et al, 2017). These tests help by allowing the reporter to state whether the changes in the cells are more likely to be transient rather than to go on to develop to high grade disease.

Human Papillomavirus (HPV)

HPV comprises over a 100 sub-types of which 40 affect the female genital tract but it is the high-risk sub-types mainly

HPV 16 and 18 that are the principle cause of CIN – the premalignant changes found in the cervix and cervical cancer (Walboomers et al, 1999: Bosch et al, 2002).

The NHSCSP always assesses new methodology to ensure this technology such as HPV testing, molecular markers and scanning techniques will improve the sensitivity and specificity of screening but still remains cost-effective. There have been many studies confirming that using HPV testing offers better sensitivity for the detection of precancerous changes and is able to identify women who may go on to develop cervical disease particularly if they have been diagnosed with a low grade cytological abnormality (Arbyn et al, 2005: Kitchener et al, 2009: Ronco et al, 2010: Murphy et al, 2012). When reviewing the literature, it needs to be considered what the authors are basing their conclusions on as the clinical outcomes can be matched to CIN 2+ or CIN 3+ cut off which may bias the results in to looking more sensitive.

As stated earlier, although the literature suggests that new tests in the cervical screening programme may be superior, the English programme will always assess new tests within the confines of the NHSCSP and with the overview of the Advisory Committee for Cervical Screening (ACCS). The ACCS is comprised of experts covering all aspects of the English cervical screening programme including GPs, senior biomedical scientists, Consultant Histopathologists, Epidemiologists etc. that are accountable to the UK National Screening Committee (NSC). The UK NSC provides guidance and advice to the Department of Health about all screening programmes in the four nations. The NHSCSP pilots the new tests through six cervical screening laboratories (Bristol, Liverpool, London,

Manchester, Norwich and Sheffield) known as the sentinel sites and the results are evaluated to shape the future direction of the programme.

The first pilot in 2008 looked at the implementation of HPV triage and test of cure (ToC) to evaluate whether this would work in the English screening programme. The literature was suggesting that combining cytology and HPV tests should speed up the referral of women for colposcopy, reduce the number of re-tests, return women to normal recall earlier, avoid unnecessary referrals for colposcopy and is cost-effective (Manos et al, 1999: Legood et al, 2006). Women who are not infected with high risk HPV are virtually at no risk of developing cervical cancer in the next ten years with a negative predicative value of just under 100% (Safaeian et, 2007: Fröberg et al, 2008). Women who are on annual follow up for ten years after treatment for cervical disease can be returned to normal recall if they are HPV/cytology negating all the anxiety of repeat cytology and reducing the time span of the patient pathway.

As a result of this successful pilot, HPV triage and ToC was successfully rolled out nationally in 2011 (Department of Health, 2011).

Human Papillomavirus (HPV) vaccination

The Cancer Reform Strategy (Department of Health, 2007) announced that the HPV vaccination would be introduced to school girls from 2008 to protect them from the high risk HPV types 16 and 18 and significantly reduce their risk of developing cervical cancer. This has now been expanded to include boys of school age too, to commence in September

2019 (Department of Health and Social Care, 2018). Studies have shown that the introduction of the HPV vaccination may prevent up to 70% of cervical cancers from developing, however cervical screening will still be needed to detect premalignant changes for cancers which will not be prevented by the HPV vaccine (Muñoz et al, 2003: Howell-Jones et al, 2010). This means that vaccinated women will have less CIN which will decrease the sensitivity and specificity of cytological cervical screening with microscopic assessment - in other words, the less you see of the precursors for disease such as abnormal cells, the less likely you are able to identify them (Evered, 2010). Due to this risk, alternative screening strategies will need to be developed and implemented before the first cohort of vaccinated women come through for screening hence why the NHSCSP has implemented HPV primary screening which is described next.

HPV Primary Screening

Following on from the successful introduction of HPV triage and ToC, the NHSCSP used the sentinel sites to evaluate the introduction of HPV primary screening. The evaluation was based on the outcomes of four major European randomised trials including the English study 'A Randomised Trial in Screening to Improve Cytology' the ARTISTIC trial (Bulkmans et al, 2004; Naucler et al, 2007; Ronco et al, 2010, Kitchener et al, 2009 and Kitchener et al, 2009b). The ARTISTIC trial showed HPV testing was more sensitive for the detection of cervical disease than cytology alone and a negative HPV test gave longer protection which may allow for screening intervals to be extended (Kitchener et al, 2009). Further screening

rounds in the ARTISTIC trial demonstrated that the screening intervals could be extended and HPV primary screening would be more cost-effective (Kitchener et al, 2014)

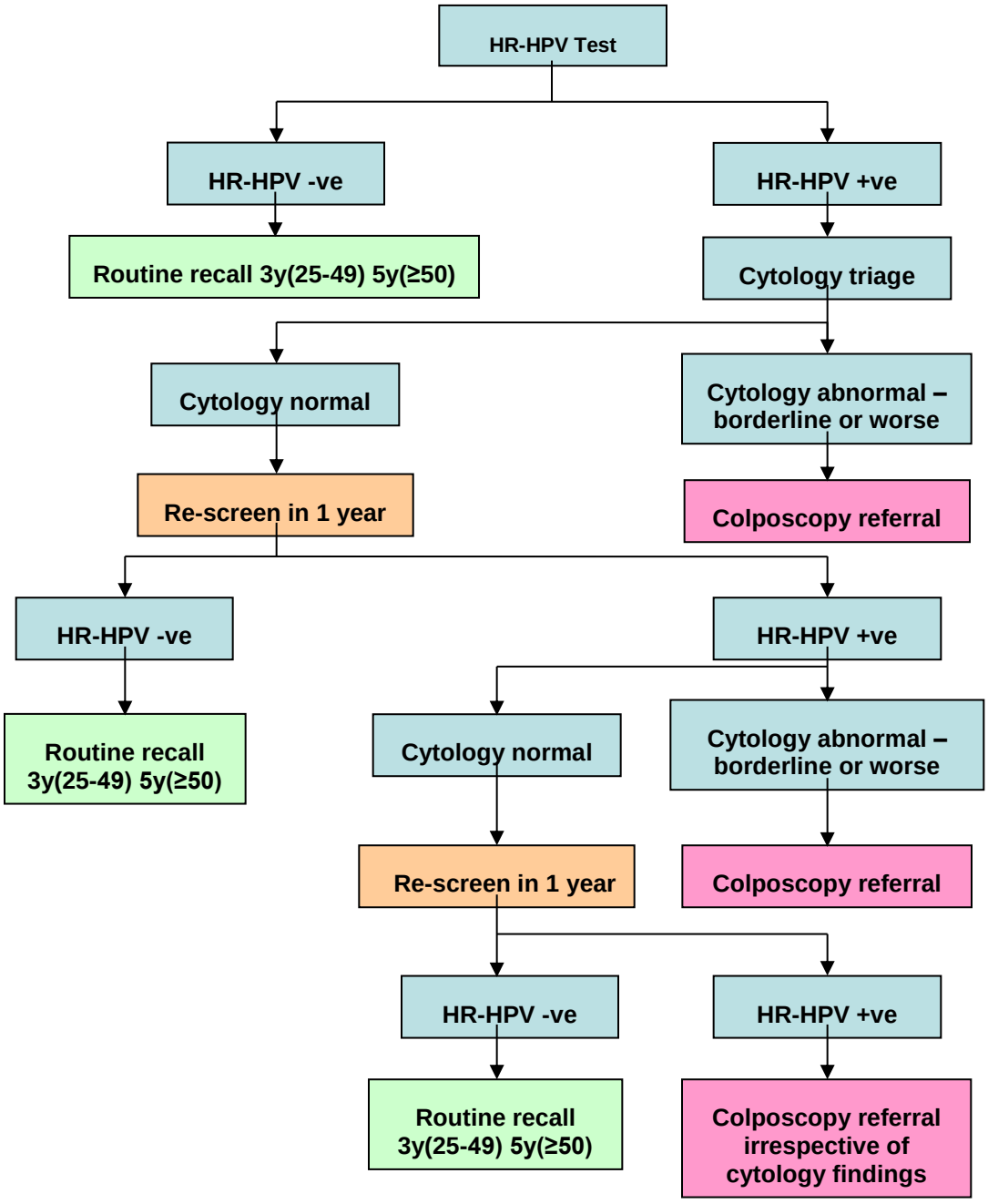
England was one of the first countries to introduce HPV primary screening. With HPV primary screening the sample is taken in the same way with cells scraped from the surface of the cervix using the NHSCSP approved brush. Depending on which LBC technology is used, the brush is left in the vial as with SurePath™ or with ThinPrep® the cells are deposited in the vial. The change occurs at this stage, as the vial is tested for HPV first and if negative, the woman is returned to normal recall. If the HPV test is positive, a slide is prepared for microscopic assessment. If the cytology slide is negative, the test is repeated in 12 months and if positive i.e. abnormal cells found, the woman is referred for colposcopy for further assessment. The HPV primary screening protocol is shown in Figure 4. The results of the pilot sites demonstrated that HPV primary screening was acceptable to the programme. The UK NSC recommended that HPV primary screening should be rolled out nationally and it was formally announced in 2016 by the Public Health Minister, Jane Ellison (Department of Health and Social Care, 2016).

There will be major implications for the NHSCSP and workforce in the cervical cytology screening laboratories. The HPV test is performed first on a high throughput automated platform and the cytology slides are prepared on the HPV positive samples meaning there will be fewer slides to screen. In the

observational study where the six pilot sites undertook HPV primary screening, the overall HPV positivity rate was found to be 12.7%, however in Sheffield the positivity rate was 16% (Rebolj et al, 2019). This means in a workload of 100,000 samples approximately 13,000 slides will be produced. On the back of the reduction in screening slides and high throughput HPV testing platforms, the decision was made to move from 46 laboratories to larger centres which was originally 10 to 15 or 4 to 5 based on the options appraisal (Public Health England, 2017). The announcement in October 2018 stated there would be a maximum of 13 laboratories however in the final notification of tender there were a maximum number of nine lots (Public Health England, 2018). As there will be less screening centres, this will have an increased impact on the cytology workforce and their inability to move to these areas.

Any woman who is found to have an abnormality from her cervical cytology and HPV test is referred to colposcopy for further investigation as part of the NHSCSP aims to prevent cervical cancer.

Figure 4 Protocol for HPV Primary Screening



Colposcopy

Women are referred for a colposcopic examination if there are clinical grounds such as abnormal bleeding including postmenopausal bleeding, post-coital bleeding, a suspicious looking cervix or through the cervical screening programme where they have had an abnormal cervical screening test such as high-grade dyskaryosis.

The colposcope was developed by Hans Hinselmann in 1925 to visualise the cervix plus the vagina and vulva utilising optimum illumination and magnification (Fusco et al, 2008). This medical procedure is usually performed in an out-patient setting. The woman is examined in the lithotomy position and a speculum is inserted in to her vagina (Figure 5).

This allows the cervix to be visualised through the colposcope and the magnified view enables the colposcopist to identify whether there is any cervical abnormality which requires treatment or the examination may reveal there is nothing wrong. To help with the examination, dilute acetic acid solution and Lugol's Iodine are applied to the cervix to look for characteristic patterns which may indicate pre-cancerous changes or cervical cancer (Shafi et al, 2002).

Acetic acid (3 or 5%) is applied to the cervix with a cotton swab and potential abnormal areas turn white, called aceto-white. The white area is caused by the acid coagulating with cellular proteins indicating higher nuclear density associated with precancerous lesions. Once the acetic acid is applied, the aceto-white change is graded 1 to 3 depending on the how quickly and the degree of onset of whiteness. This allows the colposcopist to give an opinion as to the grade of possible

abnormality i.e. low grade or high grade (Palmer, 2010). The quicker the uptake of acetic acid and the more intense the whiteness, the more likely the higher the grade of cervical neoplasia.

Figure 5 Colposcopy Procedure

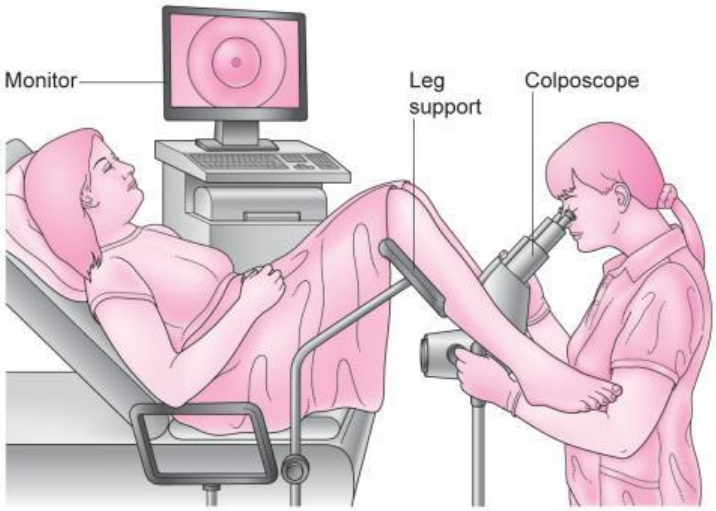


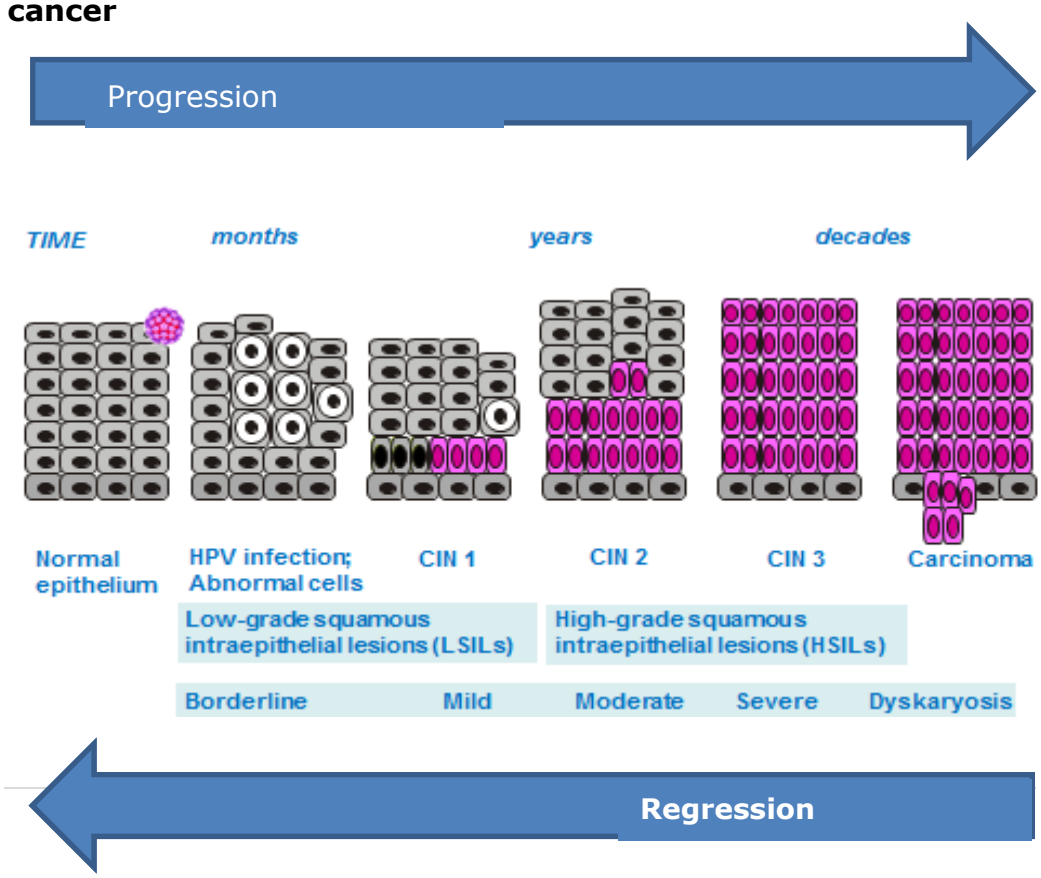
Image courtesy of Jo's Cervical Cancer Trust ©

If the colposcopist is unsure they will take cervical biopsies to confirm whether there is any abnormality or not. It is estimated that approximately 1% of CIN 1, 5% of CIN 2 and more than 12% of CIN 3 will progress to cervical cancer, thus high grade CIN is treated as we do not know which lesions will progress (Oster, 1993). If the colposcopist is certain there is high-grade present, they may do the treatment there and then in the clinic, known as 'see and treat' (Dunn et al, 2003: Cardenas-Turanzas et al, 2005). This is usually by means of a large loop excision of transformation zone (LLETZ) and in some cases they may use ablation techniques such as laser or cryotherapy (Prendiville et al, 1989).

Cervical cancer can be detected at colposcopy but may be recognised without the use of the colposcope. Features of a cervical cancer can be a large friable and ulcerated lesion and may bleed when taking a sample. If a cancer is not obvious, it can be recognised by a characteristic mosaic and punctuation pattern after the application of acetic acid plus an irregular blood vessel pattern referred to as 'corkscrews' (Palmer, 2010).

The main aim of colposcopy is to detect and treat cervical neoplasia which if not treated may develop into cervical cancer. Once HPV is integrated into the cervical epithelium it can take years to progress to cervical cancer, however as well as progressing, the disease can regress as shown in Figure 6 (Burd, 2003: Solomon et al, 2002).

Figure 6 Progression/regression of HPV with cervical cancer



Histology

LLETZ samples are sent to the histopathology department for processing and to confirm the successful treatment of cervical disease. As cytology is the microscopic assessment of cells, histology is the microscopic assessment of cells within the tissue and organ structure. Histopathology is the microscopic assessment of disease of tissue/organ samples and provides a critical role in the diagnosis of cancer. Specimens can include anything from skin biopsies – small samples from the skin, gross specimens such as the appendix, kidney and amputation specimens such as a leg. Samples can be sent fresh for the laboratory to control the fixation of samples or in pots with formalin. Formalin is comprised of 10% formaldehyde with buffers and water known as 10% neutral buffered formalin (NBF) (Bancroft, 2019). 10% NBF preserves the structure of the tissue and cells and also hardens the tissue for further processing by cross-linking proteins.

Specimens are given a unique number on receipt in the histology laboratory which is linked to the patient that the sample came from. Specimens can be processed whole or in the case of LLETZ specimens, they will be dissected and placed in cassettes for processing with their unique number for identification. Samples from the specimen are processed by removing water using ascending grades of alcohol, into a clearing agent usually xylene which is miscible with both alcohol and wax. This is usually done overnight and when finished the tissue samples are embedded in a wax block which

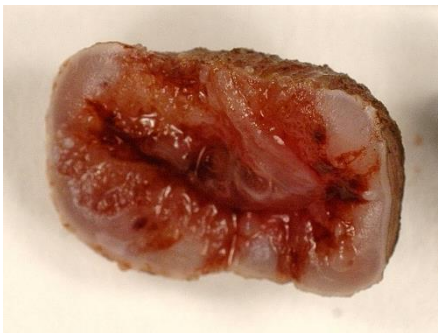
supports the tissue when it is cut with a microtome. Thin slices of tissue are cut called sections which are 4 micrometres thick, floated on a water bath and picked up with a glass microscope slide. When the section has dried on to the slide labelled with the unique number, it is ready for staining. The section is rehydrated going through xylene and descending grades of alcohol back to water. The routine stain in the histology laboratory is haematoxylin and eosin (H&E) as it is easy to use, automate and is an overall good stain for general tissue structures (Bancroft, 2019). The stained slide is looked at down the microscope and is usually examined by a Histopathologist to interpret the cell structures and give a diagnosis.

Cervical Samples from Colposcopy

There are mainly two types of samples that are received from colposcopy to be diagnosed by the Histopathologist as part of the NHSCSP. A cervical biopsy is a procedure that is done at colposcopy and is an out-patients procedure. When the colposcopist examines the cervix and identifies an area which may be potentially abnormal, they will remove a small sample of tissue for histological examination – the cervical biopsy. The colposcopist will have formed their opinion as to the grade of abnormality; however the histopathology report will give the correct grade of abnormality if it is present. This is a diagnostic sample to confirm if there is the presence of precancerous cervical disease or not and whether the patient needs treatment or not. The most popular form of treatment is the large loop excision of the transformation zone (LLETZ).

LLETZ is the treatment of choice to treat women with high-grade disease such as CIN 2 or CIN 3 plus cervical glandular intraepithelial neoplasia (CGIN). This procedure is usually done in an out-patients' setting as it is easy to perform, inexpensive and quick (Prendiville et al, 1989: Martin-Hirsch et al, 2002). Local anaesthetic is applied to the cervix and an electrified hot wire loop is passed through the cervix incorporating the transformation zone to remove the whole area of disease. The loop cuts the tissue but also cauterises the blood vessels minimising bleeding. A piece of cervical tissue is obtained which is sent for histological examination to assess any cervical disease present, check there is no cancer present and if the margins are clear of disease.

Figure 7 Fresh LLETZ specimen



Colposcopy Multi-disciplinary Team Meetings (MDTs)

Colposcopy MDTs are held between representatives from cytology, histology and colposcopy plus the cervical screening provider lead (CSPL) who oversees the quality and performance of the cervical screening programme in each Trust. They meet to discuss any cases where there are

discrepancies and mismatches between any of the findings e.g. high grade dyskaryosis on cervical cytology but the histology shows CIN 1. All the slides and histories are reviewed to see if the original diagnosis is still valid in view of further clinical information. The team discuss the reviews and agree on a suitable management regime for each of these patients. Other cases that are discussed are women who are being managed conservatively or women with CGIN to ensure that they have appropriate follow up. These meetings must be held at least once a month with all colposcopists attending at least 50% of them (Public Health England, 2016).

Cervical intraepithelial neoplasia (CIN)

The features to identify abnormalities on cervical cytology are very similar to those found to diagnose CIN on histology preparations (NHS Cervical Screening Programme, 2012). The NHSCSP uses a three tier system of reporting CIN which correlates with the three tier reporting of cervical cytology and reflecting that the development of cervical intraepithelial neoplasia as a continuous process – see Figure 8. This is opposed to the Bethesda System which is a two tiered system of reporting – low and high intraepithelial lesions (Nayar and Wilbur, 2014)

Figure 8 Progression of CIN to cervical cancer

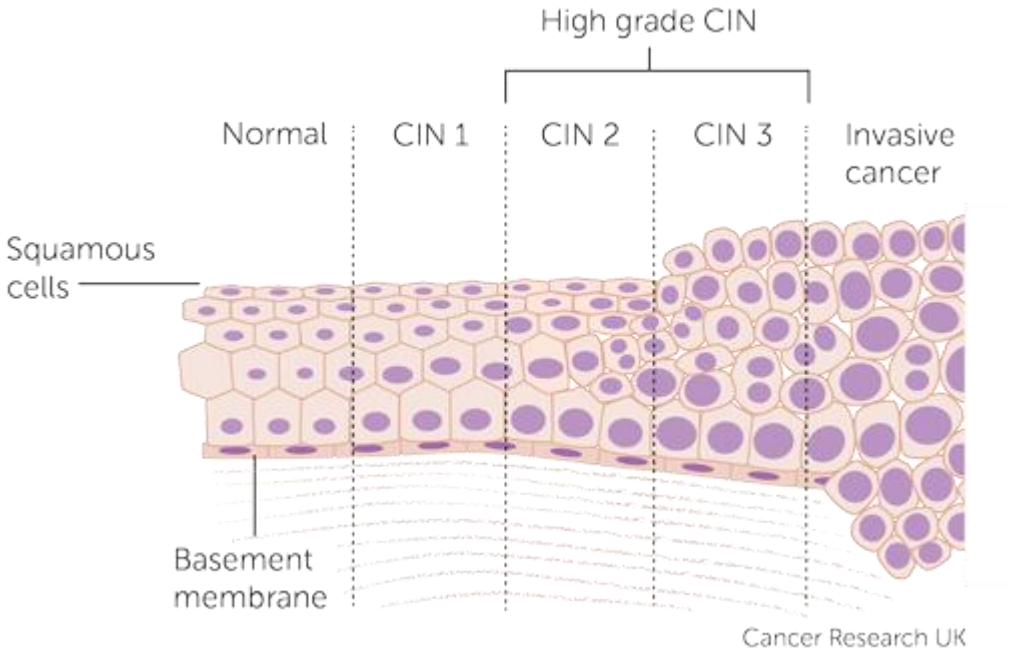


Image courtesy of Cancer Research UK (2019)

Nuclear abnormalities are key features for the diagnosis of dyskaryosis in cytology and CIN in histology. Both histology and cytology abnormalities of the cervix share similar characteristics for microscopic diagnosis. Assessment is made on the nuclear atypia such as the irregularity in size, clumping of chromatin and the nuclear to cytoplasmic ratio. The more pronounced these changes the higher the grade of severity. Mitotic activity is an indication of cell activity and possible development of cervical abnormality. These features are seen in the epithelium of the cervix which helps with the diagnosis of CIN whereas in cytology you have to interpret the variation within the cell groups and individual cells to determine the

degree of dyskaryosis (NHS Cervical Screening Programme, 2012).

There are three grades of CIN that affect the squamous epithelium of the ectocervix (see Figure 2) before the lesion develops in to a cancer. The recognition of CIN is subjective and is diagnosed based on characteristic features and patterns. The grading of CIN is based upon the depth of epithelium that is affected by undifferentiated neoplastic (abnormal) cells, where in the epithelium mitotic figures are identified and whether the mitotic figures are abnormal or not (Institute of Biomedical Science, 2011).

CIN 1 affects the bottom third of the epithelium where the cells display nuclear atypia but mature normally through the rest of the squamous epithelium. It is rare to see any mitotic activity and these changes are usually associated with HPV. CIN 1 will often regress back to normal epithelium, however in some cases it will progress to CIN 2.

CIN 2 is diagnosed when there is an increased nuclear atypia and is seen up to the middle third of the squamous epithelium. CIN 2 may regress hence the colposcopists may manage the patient conservatively depending on her circumstances and age e.g. she may want to conceive and treatment may affect her ability to do so. By managing conservatively, this allows the colposcopist time to see if the disease progresses or not, helping to make the judgement as to whether treatment is

appropriate (Prendiville, 2009). The final third of epithelium matures normally. Mitotic figures may be seen in the lower two thirds of the epithelium and there may be abnormal mitotic figures through these layers.

CIN 3 is the last classification of disease before cancer is diagnosed and the nuclear atypia is seen through the full thickness of squamous epithelium. There is more severe nuclear atypia associated with CIN 3 and abnormal mitotic figures throughout the epithelium.

Cervical glandular intraepithelial neoplasia (CGIN) is the precancer of the glandular epithelium of the cervix seen in Figure 2 as the endocervix. CGIN features nuclear atypia which forms multilayers in the single layer of glandular epithelium called pseudostratification.

Cancer is diagnosed if the abnormal cells have broken through the basement membrane of the squamous epithelium and invaded in to stromal tissue below. The stages of cervical cancer are classified by the International Federation of Gynaecology and Obstetrics (FIGO) (Bhatla et al, 2019).

Margins

The detection of cervical disease at the margins may be an indicator of treatment failure with a possible recurrence and may suggest that the woman needs further treatment (Manchanda et al, 2008). There are three margins present on

a LLETZ specimen – ectocervical, endocervical and deep lateral margin which are illustrated in Figure 9. Recurrence is higher with women who have high grade disease and if it is found at the deep lateral margins and/or endocervical margins (al-Nafussi and Hughes, 1994). In Arbyn's met-analysis of incomplete excision of cervical precancer as a predictor for treatment failure, it was found that overall there were 23.1% of women (total women 44,446) that presented with positive margins with the overall risk of residual or recurrent disease found to be 6.6%. These are not insignificant numbers/risk and require follow up (Arbyn et al, 2017).

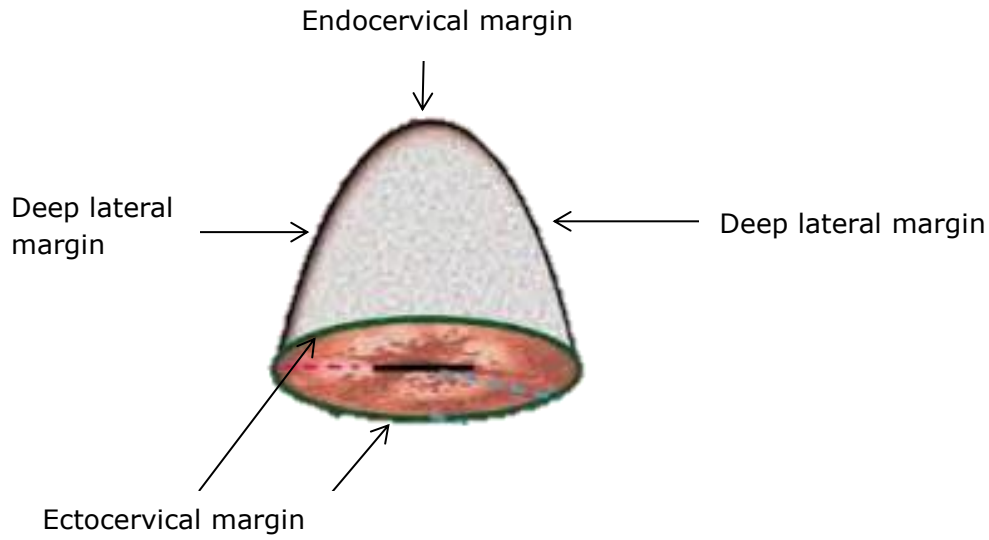
It is important that the person reporting the LLETZ is able to identify the margins and report whether these are involved with cervical disease or not. There will be some clearance as the treated area of the cervix has undergone destructive treatment with diathermy and many colposcopists go over this area with a diathermy ball. The recommendation is to paint the margins of the LLETZ with different coloured inks to help the identification of these when examining the sections down the microscope (NHS Cervical Screening Programme, 2012).

HPV

HPV with associated koilocytes is reported histologically even though it is a benign condition and is included as part of the RCPath minimum data set. This is because the cytological findings of borderline or low grade dyskaryosis may be explained by the presence of HPV (koilocytes) in histological

sections from cervical biopsies/LLETZ classified as mismatches at the Colposcopy MDTs. Histological features of HPV (koilocytes) are identified by cells with nuclei having a 'wrinkled' outline with slight enlargement but a regular chromatin pattern. The cytoplasm of these cells is vacuolated with a clear hard rim around the edge. Koilocytes are mostly found in the upper superficial layers of the epithelium. If any koilocytosis is found associated with CIN, the CIN must be graded and reported as defined in the NHSCSP guidelines (NHS Cervical Screening Programme, 2012).

Figure 9 Diagram to illustrate the margins of a LLETZ specimen



Modified image courtesy of efccolposcopy.eu

Introduction of Histopathology Reporting by Biomedical Scientists

During the time this study was being written up, RCPath and IBMS have issued a joint statement regarding the development of BMS reporting histopathology. A working party from the RCPath and IBMS began the discussions in 2010 and the first BMS entered the histopathology reporting pilot in 2012 (Horne et al, 2018). This development has followed on from the success of BMS reporting abnormal cervical cytology and ophthalmic pathology and is a natural progression for BMS delivering specimen dissection. This role has also been developed due to a chronic shortage of Histopathologists in the UK and in order for this to succeed, the barriers concerning traditional roles between BMS and Histopathologists need to be broken down. There has been a reluctance of many Consultant Histopathologists to accept that non-medically qualified scientists can report histopathology if they have had the appropriate training and are deemed competent (Liebmann et al, 2015). I have also found resistance to change within my own Trust and it is mainly the 'traditional' pathologists that are reluctant to support any training or change of roles.

The areas of histopathology that were chosen as part of the initial pilot were gastrointestinal and gynaecological pathology. This was on the basis that these areas represent high workloads with a low risk of litigation, lower complexity and contribute to backlogs within departments (Liebmann et al, 2015). To be eligible for training in gynaecological pathology

reporting, the biomedical scientist must be registered with HCPC, be a Fellow (FIBMS) or Member (MIBMS) of the IBMS and have at least seven years post-registration experience in cellular pathology, although this has recently been reviewed and put down to 5 years (IBMS and RCPath, 2017). The BMS must have the support of their Trust and the Medical Head of Department with a suitably qualified named pathologist to be the workplace based supervisor. In order to be accepted on the training programme, any prospective candidate has to attend for an interview with a panel of members from the RCPath and IBMS.

The curriculum mirrors the curriculum that is presented to histopathology trainees in their first year. It is an extensive programme covering the dissection and reporting of the female genital tract. The training programme is in four stages and is expected to take a minimum of four years. There is a general expectation that the BMS will do this training above and beyond their normal working duties which is very different from what is expected from the trainee pathologists. Trainee pathologists are supernumerary with dedicated time to train and study in their workplace. As most BMS are already very busy with their own day to day roles making time to study has proved extremely difficult for them to achieve and they have had to commit to working weekends and after work to keep up with the training programme. This was confirmed in a questionnaire that RCPath and IBMS undertook in 2017 as there has been quite a high dropout rate (Nation, 2017). As a

result of these findings, the conjoint board is recommending that departments should allow the BMS some protected time for their training.

Advanced Specialist Diploma (ASD) Histopathology Training Programme

The first year (Stage A of the curriculum) introduces the BMS to histopathology with the focus on gynaecological pathology. They are expected to be competent in the cut up of simple specimens such as LLETZ plus larger simple specimens such as benign hysterectomy samples. They must be able to demonstrate that they can write up reports for appropriate histopathology specimens and are able to manage their time. To successfully complete their training and move on to Stage B, they have to submit a portfolio and pass an exit examination. The portfolio must include evidence of reporting a minimum of 750 cases, audits and an interesting case report. There will also be evidence of at least 18 assessments in the workplace and regular feedback from the supervisory pathologist. The portfolio is assessed at the end of the year and if they pass the examination, they can move on to the next stage.

The next stages B and C follow on from stage A and introduces the BMS to more complex cases and gynaecological cancers. They must report a minimum of a 1000 cases and demonstrate their progress reporting more complex cases in their portfolio

which is submitted at the end of the year. The BMS passes onto stage C if their portfolio assessment passes strict criteria as there is no formal examination at the end of this year. Stage C continues the theme of reporting more complex cases and includes an exit examination including practical tests such as dissecting specimens and reporting cases. After successful completion of stage C and passing the exit examination the BMS will be awarded with the RCPath/IBMS Advanced Specialist Diploma in Histopathology Reporting (Gynaecological pathology).

The final part of training is stage D which is a consolidation of all the knowledge and skills that have been learnt through the previous stages and prepares the BMS for independent reporting. The supervising pathologist develops a reporting plan to aid the BMS to become an independent practitioner. Once appointed to the role of histopathology reporting, the BMS will work with medically qualified consultants as part of the reporting team covering all the roles they do such as dissection, reporting and presenting cases at multidisciplinary meetings. They will perform audits, train junior staff and participate in appropriate external quality assurance schemes (IBMS and RCPath, 2017).

Pilot study of Consultant BMS reporting large loop excision biopsies of the cervical transformation zone (LLETZ)

As described earlier, Consultant BMS who report cervical cytology are highly skilled in the interpretation of cellular morphology with an extensive knowledge of the cervix (Smith, 2009). In Sheffield, it was realised that there was a potential to utilise these skills to the benefit of the Histopathology department allowing the Histopathologists to concentrate on the more complex gynaecological cases.

LLETZ samples were chosen for this pilot study as they form a big proportion of the routine workload for a Gynae Histopathologist with plenty of material to interpret. In the majority of cases in Sheffield, a woman is treated with a LLETZ if her preceding cervical biopsy showed CIN 2 or above, although the 'see and treat' policy is gaining favour as it can be done in one visit to colposcopy being better for the patient and more cost-effective (Dunn et, 2003). As in the majority of cases, there is a preliminary diagnosis made from a previous cervical biopsy, hence LLETZ samples are seen as clinically low risk and is the method of treatment after the diagnosis of high grade CIN/CGIN.

For the clinician, the report generated by the Histopathologist should address the following issues (NHS Cervical Screening Programme, 2012).

- What is the grade of CIN - does it correlate with the biopsy if taken plus the colposcopic and cytology findings
- Is there any evidence of invasion suggesting a possible cancer?
- Are the margins clear as if not may suggest further excisional treatment may be required?

The reporter needs to take into account the size and the volume of the high-grade lesion plus involvement of the disease into the crypts as this may be suggestive of a possible risk of invasive cervical cancer (al-Nafussi and Hughes, 1994: Ostör, 1993 and Tidbury et al, 1992)

Original Pilot Study of LLETZ Reporting by Consultant BMS in Sheffield

In the original pilot study, two Consultant BMS 'shadow reported' LLETZ specimens. This involved my colleague and me reporting the LLETZ specimens in 'real time' before they were finally reported by Dr Branko Perunovic (BP), Consultant Histopathologist. 104 LLETZ specimens were assessed and according to standard local practice, they had a previous diagnosis of CIN confirmed by cervical punch biopsy prior to the procedure. Each specimen was cut in 3mm parallel slices and each slice was embedded in a separate block which was sectioned at three levels at 80-100μm intervals. All the cases were reported by BP with his conclusions used as the 'gold standard' for comparison.

Table 2 Final diagnoses in 104 cases of LLETZ biopsies

Three tier system	No	%	Two-tier system	No	%
Negative	9	8.7	Negative	9	8.7
HPV only	11	10.6	LSIL	14	13.5
CIN1	3	2.9			
CIN2	14	13.5	HSIL	76	73.1
CIN3	62	59.6			
High-grade CGIN	2	1.9	AIS	2	1.9
Invasive carcinoma	3	2.9	Invasive carcinoma	3	2.9

The 104 cases as seen in Table 2 were independently examined by the two Consultant BMS (KE, ND) and our diagnosis was based only on our previous knowledge and experience. Although we were both experienced cytologists, one of us had practically no experience in interpreting histology, whilst the other had gained a limited experience in interpreting histology prior to this study by participation in preparation for multidisciplinary team meetings and research.

We used pro-forma reports compliant with the RCPath minimum data set, thus the comments were restricted to

stating the presence or absence of all of the following histological findings:

- Cervical Intraepithelial Neoplasia (CIN) – 1-3
- Cervical Glandular Intraepithelial Neoplasia (CGIN)
- Histological hallmarks of HPV infection (e.g. koilocytosis)
- Invasive neoplasia
- Status of the ectocervical, endocervical and deep lateral margins of excision.

The results from the Consultant BMS reports were compared to those in the final report and the inter-observer variations for grading of CIN were calculated using *kappa* (κ) test. This evaluation also included assessment of the inter-observer correlation in regards to *two-tier* system for grading of Squamous Intraepithelial Lesions (SIL), with HSIL comprising lesions designated as CIN 2 and CIN 3 in the three-tier system, whilst the diagnosis of LSIL included CIN 1 and lesions showing evidence of HPV infection only (e.g. koilocytosis) (Ellis et al, 2012). For Consultant BMS 1 the inter-observer agreement for each report of negative, CIN 1, CIN 2 and CIN 3 was 85.9% with κ = 0.742 and Consultant BMS 2 had inter-observer agreement of 81.8% with κ = 0.674. The inter-observer agreement of negative, low grade SIL and high grade SIL was 92.9% with κ = 0.812 for Consultant BMS 1 and for Consultant BMS 2 was 86.9% with κ = 0.658. The kappa degree of agreement is explained in Table 5. For the Consultant BMS their inter-observer agreement was classified

as good with Consultant BMS 1 achieving very good agreement for the SIL correlation.

When the correlation was assessed for the interpretation of margin involvement, there was more of a difference between the Consultant BMS. Consultant BMS 1 had an excellent agreement with the Histopathologist regarding the endocervical, ectocervical and deep lateral margins of excision (κ = 0.942, 0.864 and 1.0 respectively). Consultant BMS 2 showed a much lower level of agreement with (κ = 0.635, 0.561 and 0.013 respectively). I concluded that the difference was due to previous experience in a histopathology laboratory and I recognised LLETZ samples as 3-dimensional specimens being able to recognise margins.

Histological evidence of HPV infection was assessed. There was found to be very good inter-observer agreement between the Histopathologist and Consultant BMS 1 with a κ agreement of 0.946 and with Consultant BMS 2 this was only fair at a κ agreement of 0.301.

As there was good correlation between the Consultant BMS and the final reports issued by the Histopathologist, I decided to expand the remit of the pilot study. The plan was to recruit more Consultant BMS from the UK and to see whether these promising results could be replicated wider. If a Consultant BMS was allowed to report LLETZ within the confines of the NHSCSP, this would allow Consultant Histopathologists to

concentrate on the more complex and cancer gynaecological specimens providing a more timely and cost-effective service for women and the NHS.

As this study has been on-going the conjoint board of the IBMS and RCPath have introduced the ASD in Histopathology Reporting in Gynaecological Pathology/ Gastrointestinal Tract (GIT) Pathology. The training programme associated with the ASD in Histopathology Reporting takes a minimum of four years. This ASD will be reviewed in line with my proposal of reporting restrictions to LLETZ specimens only instead of all gynaecological samples. This will be a module specific to LLETZ specimens as opposed to the full curriculum for gynaecological pathology.

Methods

Recruitment of Volunteers

As stated earlier, the original pilot showed very promising results but only involved two Consultant BMS. To continue the development of this work, I applied to the Trust's NHS Research Ethics Committee (REC) and was granted permission to continue the work – the study was registered as 'STH14976 ABMSP LLETZ Reporting'.

The data from the original pilot of myself and my colleague was presented at the IBMS Congress in 2009 (Appendix A) and the International Academy of Cytology (IAC) scientific meeting in Edinburgh 2010. As part of the presentation at the IBMS Congress and through the Consultant BMS network, volunteers were asked to come forward to extend the study to include more Consultant BMS within the UK. Once I got approval, Dr Branko Perunovic, the Clinical Director for Laboratory Medicine and Gynaecological Histopathologist at Sheffield Teaching Hospitals was my supervising pathologist for this work. We designed a structure for how the study would work.

BMS who volunteered ideally should have the ASD in cervical cytology however one of the volunteers had extensive experience of specimen dissection in histology with a particular interest in cervical specimens. It was important that the BMS had microscopy experience and knowledge of cervical disease as this would help with their interpretation of the cases. It was paramount that they had the support of a Histopathologist

based in their workplace to mentor and guide them through the process of reporting. As part of the recruitment process and if feasible, Dr Perunovic and I visited the volunteer BMS together with their pathologist mentors to explain how the study would be managed and what was expected of them. Volunteers were expected to undertake the reporting in their own time and there was no funding associated with this study.

Nine Consultant BMS volunteered to take part in this study which included me plus one senior BMS who was not a cytologist but as stated earlier, had vast experience in histopathology and the dissection of specimens. Four of the Consultant BMS had a background that included previous experience of working in a histology laboratory and five had a purely cervical cytology background however they were exposed to reviews of LLETZ samples at Colposcopy MDTS. Of the original nine, only six Consultant BMS managed to complete the full set of slides. The other three Consultant BMS were unable to continue with the study due to work commitments and time restraints. I felt that there was not enough data from them to contribute to the overall results for the study as they had only completed between six to 30 cases. The BMS with dissection experience had to decline to take part too, due to time commitments and personal reasons. A training day was arranged for the interested BMS so that they could get an idea of what was expected of them.

Training Day

The training day was held approximately a month before the proposed start date led by Dr Branko Perunovic who was the overall supervising pathologist and my workplace mentor based at the Royal Hallamshire Hospital, Sheffield. The training programme (Figure 10) gave an overview of how the pilot was to operate and included a video of how LLETZ specimens arrived in the histopathology laboratory. The video demonstrated how the LLETZ specimens were measured and dissected to obtain histological slides to examine under the microscope. The video was important to explain to the Consultant BMS how sections of the LLETZ were orientated in the blocks and how the margins presented. If any premalignant disease is present at the margins, there is the possibility that the lesion may not have been fully excised and a repeat procedure may be required.

The next part of the training programme was a multi headed microscope session with examples of normal histology of the cervix, the premalignant phases of cervical cancer called CIN and CGIN, invasive cervical cancers and finally difficult to interpret benign conditions such as microglandular hyperplasia versus premalignancy of the cervix (NHS Cervical Screening Programme, 2012). This session also covered slides where the section had been cross-cut and where there was diathermy artefact at the margins of the LLETZ which may cause the Consultant BMS problems in interpretation. The final stage was a self-assessment session where individuals were given a

set of slides with various stages of cervical disease - benign, premalignant and cancer for them to give a histological diagnosis and was followed up by a multi-header microscope session to review these cases.

Figure 10 Training Programme for Consultant BMS

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

PROGRAMME FOR SHADOW REPORTING OF LLETZ SPECIMENS TRAINING DAY FOR ADVANCED BIOMEDICAL SCIENTIST PRACTITIONERS (ABMSPs)

9.30 am	Coffee	
10.00 am	Introduction To include background, format and protocol	KE
10.20 am	Training session	BP
	Multiheaded discussion of basic problem areas Wart virus v 'look-a-likies' Atrophy and thin epithelium Reactive metaplasia/repair Early stromal invasion v CIN in crypts Grading – 'stripped' epithelium - problems of cross cutting - equivocal CIN CGIN v TEM Microglandular hyperplasia Invasion v CGIN Margins Orientation	
12 noon	Lunch	
12.45 pm	Self-assessment section	
1.30 pm	Review	
2.15 pm	Reporting of cases	
3.00 pm	Close	

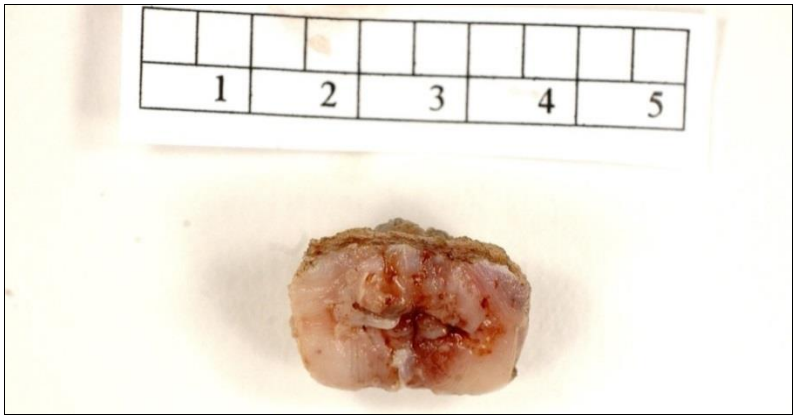
Selection of LLETZ Specimens

157 consecutive LLETZ samples from the Histopathology Department, Royal Hallamshire Hospital, Sheffield were used for this study. The number selected was based on the estimation that a trainee pathologist in Sheffield would look at 150 LLETZ specimens during their training period of general pathology of four years which would include gynaecological pathology. 157 cases were prepared for the study as detailed below and there would still be a minimum of 150 cases to compare in the event of any slides being broken or lost in transit.

Preparation of Slides from LLETZ Specimens

Each LLETZ specimen was sent to the histopathology laboratory at the Royal Hallamshire Hospital in Sheffield in a container with no fixative. Each LLETZ specimen was measured and photographed with a ruler to gauge the size of the specimen before it was placed in 10% buffered saline formalin for 24 hours to fix in preparation for dissection (Figure 11). Any separate specimens that were received in the same container were also noted on the request form, measured and fixed too.

Figure 11 Fresh LLETZ specimen



After 24 hours of fixation with 10% formalin, the LLETZ sample was dissected and cut into sequential 3mm parallel slices as outlined in NHSCSP guidance (NHS Cervical Screening Programme, 2012). Each slice of the LLETZ was placed with the cut surface, face down in to the appropriately labelled cassette, however the last block was reversed so that block had its cut surface face down, known as 'bookending'. For example with Figure 12, A to D were embedded face down and the final block E was turned the other way so that it's cut surface was face down.

Each slice was embedded into a separate cassette to create a wax block labelled with its unique histology number. It is important that the final reporter understands how the specimen had been sliced and arranged in cassettes so that they could identify the margins on examination down the microscope. If there was concern that there was disease in the end block such as E in Figure 12, the block could be melted down and embedded the other way up.

Figure 12 Fixed LLETZ specimen dissected and labelled

Each LLETZ sample was processed to wax overnight on the Sakura VIP 5, one of the automated tissue processors on the following schedule (Table 3).

Table 3 Routine processing schedule on Sakura VIP 5

Reagent	Time	Vacuum/Pressure	Temperature	Agitation
Formalin	0	On	Ambient	Fast
70% IDA	30mins	On	Ambient	Fast
95% IDA	30mins	On	Ambient	Fast
99% IDA	30mins	On	Ambient	Fast
99% IDA	1hr	On	Ambient	Fast
99% IDA	1hr	On	Ambient	Fast
99% IDA	1hr	On	Ambient	Fast
Xylene	1hr	On	Ambient	Fast
Xylene	1hr 15mins	On	Ambient	Fast
Xylene	1hr 15mins	On	Ambient	Fast
Paraffin Wax	1hr	On	60°C	Fast
Paraffin Wax	1hr 15mins	On	60°C	Fast
Paraffin Wax	1hr 15mins	On	60°C	Fast
Paraffin Wax	1hr 15mins	On	60°C	Fast

The tissue goes through a series of graded alcohols, xylene and finally paraffin wax. The graded alcohols get more concentrated as they remove water from the tissue and xylene is classed as a 'clearing' agent as it is miscible with both alcohol and wax. Xylene replaces the alcohol in the tissue before it is replaced with molten wax. The wax impregnated tissue is embedded into a bigger block of molten wax which gives the tissue stability and rigidity to allow the tissue to be sectioned without damage or distortion (Orchard and Nation, 2011: Bancroft and Gamble, 2007).

Each block from the LLETZ sample was trimmed on a microtome so that there was a full face of tissue. The blocks were kept cool on ice which makes them easier to cut and reduces artefact such as shattering marks which may affect the microscopic interpretation. Once the full face was established, a section was taken at 4μm and floated on a water bath just below the melting point of the wax to enable the section to flatten out. The best section was picked up on a glass microscope slide with that case's unique laboratory number and for the purposes of this study, the next section in the ribbon was taken known as a serial section. As the study section was taken from the same ribbon as the original reported section, they are virtually identical. The block was trimmed for a further 80-100μm intervals and the aforementioned cutting and selection procedure was repeated. This meant that for each block, there were three sections and a serial section from the same ribbon was taken at the same

time. Using Figure 2 as an example, it would mean that there were five sections (A to E) with levels 1 to 3 that were replicated for the serial sections for this study. This means that there would be 15 sections on this particular case to be examined under the microscope.

Each section was dried and stained with Haematoxylin and Eosin (H&E) on the Thermo Shandon Linistain. The dyes are water based and will not mix with the wax impregnated tissue. The slides undergo a reversal of the processing schedule in order to take the tissue back to water using xylene and graded alcohols. Haematoxylin stains the nucleus blue in the tissue and eosin stains the cytoplasm various stages of red. Each slide was mounted using the Sakura Tissue-Tek Film Coverslipper to produce a permanent slide for microscopy assessment.

Patient Confidentiality

Each LLETZ specimen for the purpose of this study was given a number starting from one so that patient anonymity would remain. This number was cross-referenced to the original unique histology number so that the clinical details and history could be transferred to the study request form and then be traced back to the final diagnostic report to compare the reports issued by the Consultant BMS to the report generated by the Consultant pathologist.

Study Request Form

The study request form was based on the information from the original request form but all patient identifiable data was removed to maintain patient confidentiality. The study request form included the patient's age, cervical screening history, previous histology and a photograph of the LLETZ specimen with the size of the specimen and the number of blocks taken. A request form was produced for each of the 157 cases with all the details transferred from the original request form and followed the guidelines as set down by the NHSCSP as shown below in Figure 13. Each of the forms was laminated to ensure that they were robust enough to withstand the handling of postage and packaging around the country.

Figure 13 Request Form

Sheffield Teaching Hospitals NHS
NHS Trust

SHADOW REPORTING REQUEST FORM

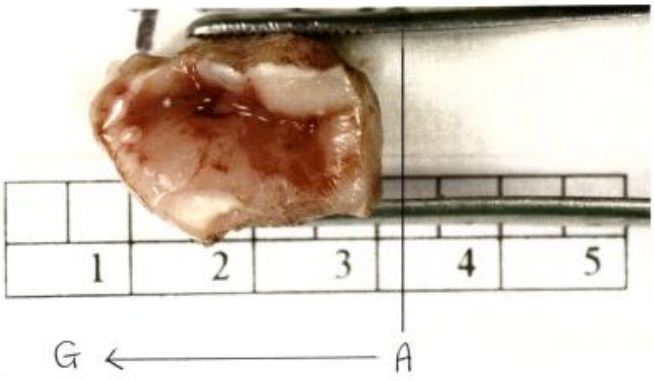
CASE 012

Age 28

Clinical Details

LLETZ

Punch biopsy showed CIN 3 LBC – Severe dyskaryosis



Macro

Loop cone biopsy of the cervix measuring 21 x 14 x 10 mm deep (blocks A-G).

Proforma Report Form

A proforma report form (Figure 14 and Figure 15) was designed for the Consultant BMS to use as a report template based on the RCPath and NHSCSP minimum dataset with tick boxes to enable easier statistical analysis (NHS Cervical Screening Programme, 2012)**.**

Each of the reporting categories on the proforma were cross-referenced to numbered codes that represented all the different disease reporting categories as seen in Table 4 based on the guidelines for Histopathology reporting in the NHSCSP (NHS Cervical Screening Programme, 2012). In Table 4, numbers have been assigned to reporting profiles where there may be dual pathology in the LLETZ such as CIN and CGIN – classified as 10. This should allow for every combination of cervical disease and aid correlation when the results were collated. This table was also extended to include whether the reporting category should be assessed as low or high grade disease of the cervix to help with analysis of results.

The design of the proforma report form also allowed for statistical analysis based on The Bethesda System of reporting using their terminology of low grade squamous intraepithelial lesion (LSIL) and high grade squamous intraepithelial lesion (HSIL) (Koss and Melamed, 2006). The proforma included whether premalignant cervical disease was present (CIN), the grade if applicable, evidence of HPV infection and whether there was any disease present at the margins. There was

space for further tests to be requested such as more levels from the histology blocks and extra stains such as immunocytochemistry to help in the diagnosis, if needed but they would not be undertaken routinely.

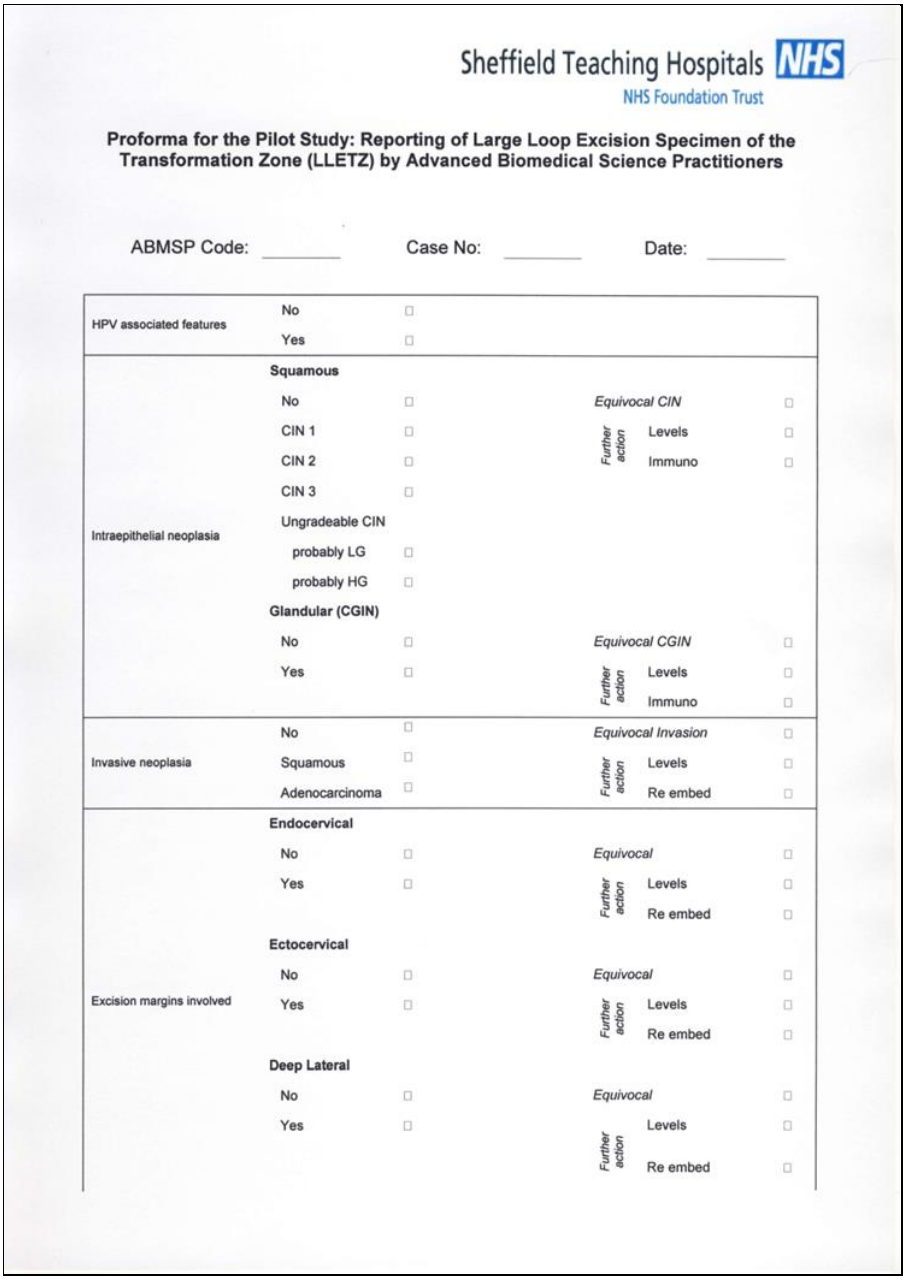
Many Histopathologists use $P16^{INK4a}$ (p16) for difficult cases to help identify whether equivocal CIN is high grade or low grade for the final diagnosis (Liu et al, 2017). Examples of other diagnostic conundrums include differentiation between florid metaplasia and CIN 3 with a positive test indicating the lesion is premalignant (Tsoumpou et al, 2009: Cuschieri and Wentzensen, 2008).

On the reverse of the proforma, there was space for any comments that the Consultant BMS may wish to put against each block number if they have had any difficulties in differentiating between premalignant cervical disease and benign mimics. The Consultant BMS reports were compared to the final histology reports issued by one of four Consultant Histopathologists that report gynaecological specimens at the Royal Hallamshire Hospital part of Sheffield Teaching Hospitals NHS Foundation Trust (STHFT).

At STHFT, all the Histopathologists are specialised into different disciplines such as gynaecology, skin, renal etc. and report these cases only. At district general hospitals, the Histopathologists are general pathologists and report on all cases that come through their department. The four Gynae Histopathologists at STHFT have at least 10 to 30 years of

experience specialising in Gynae pathology and have worked together for a long time sharing slides between them for second opinions hence their reporting is remarkably consistent. During my time working with them reviewing their cases at the Colposcopy MDT, there have been very few occasions where there have been any differences of opinion. This has been further corroborated by my role as cervical screening provider lead (CSPL) where I have to audit the history of women who have developed cervical cancer and part of this includes the review of histology. Again it was extremely rare that there were any changes of opinion between the STHFT Gynae Histopathologists.

Figure 14 Proforma Reporting Form for Consultant BMS – front page



Sheffield Teaching Hospitals NHS
NHS Foundation Trust

Proforma for the Pilot Study: Reporting of Large Loop Excision Specimen of the Transformation Zone (LLETZ) by Advanced Biomedical Science Practitioners

ABMSP Code: _____ Case No: _____ Date: _____

HPV associated features	No	☐			
	Yes	☐			
Intraepithelial neoplasia	**Squamous**				
	No	☐	*Equivocal CIN*		☐
	CIN 1	☐	*Further action*	Levels	☐
	CIN 2	☐		Immuno	☐
	CIN 3	☐			
	Ungradeable CIN				
	probably LG	☐			
	probably HG	☐			
	Glandular (CGIN)				
	No	☐	*Equivocal CGIN*		☐
	Yes	☐	*Further action*	Levels	☐
				Immuno	☐
Invasive neoplasia	No	☐	*Equivocal Invasion*		☐
	Squamous	☐	*Further action*	Levels	☐
	Adenocarcinoma	☐		Re embed	☐
Excision margins involved	**Endocervical**				
	No	☐	*Equivocal*		☐
	Yes	☐	*Further action*	Levels	☐
				Re embed	☐
	Ectocervical				
	No	☐	*Equivocal*		☐
	Yes	☐	*Further action*	Levels	☐
				Re embed	☐
	Deep Lateral				
	No	☐	*Equivocal*		☐
	Yes	☐	*Further action*	Levels	☐
				Re embed	☐

Figure 15 Proforma for Consultant BMS Reports – back page

Comments (for training purposes only, please record your findings in each block and indicate potential questions)

Block

A

B

C

D

E

F

G

H

I

J

K

L

Shadow Reporting Log LLETZ © STH Sheffield Teaching Hospitals NHS Foundation Trust

Table 4 Numbers used to identify different disease classification

Proforma Report Number	Disease representation	Cervical disease classification
0	No CIN	No disease
1	CIN 1	Low grade
2	CIN 2	High grade
3	CIN 3	High grade
4	Ungradeable CIN	High grade
5	Equivocal CIN	High grade
6	Equivocal CGIN	High grade
7	Probably low grade CIN	Low grade
8	Probably high grade CIN	High grade
9	Cervical glandular intraepithelial neoplasia (CGIN)	High grade
10	High grade CIN/CGIN	High grade
11	Squamous carcinoma of cervix (SCC)	High grade
12	Stratified mucin-producing intraepithelial lesion (SMILE)	High grade
13	Low grade CIN/CGIN	High grade

There are many reporting grades that are adopted to follow the terminology as set out in the NHSCSP Histopathology Reporting guidance. The reporting style should be clear and concise so that the clinician can interpret the report in order to

manage the patient and any subsequent treatment. For example, a woman diagnosed with CIN 2 may be managed conservatively depending on her circumstances – she may be offered ablative treatment such as laser, excisional treatment e.g. LLETZ or just put on surveillance. In a clinical setting, the reporter would review the slide with a colleague if they were unsure of the diagnosis such as a premalignant decision versus a cancer or whether there was disease present at the margins. As this was a research project, the Consultant BMS had to make their decisions independently and send their opinions back to me prior to their results being released.

To enable the Consultant BMS to get feedback and to complete their learning loop, once I had their opinions the results were released back to them while they still had the slides so that they could review them with their mentor. Some Consultant BMS took digital images of areas of the slides where they had difficulty with their diagnosis so that they could discuss with me and Dr Perunovic to get feedback as to where they may have misinterpreted the case. To reiterate, the results were only disclosed back to the Consultant BMS once I had received their opinions electronically or by paper. When I received their results, I entered them on to the central spreadsheet.

Initial review of slides by primary researcher

Dr Branko Perunovic kept the master list of original histology numbers to compare with the cases in this study. He provided the information for me to set up the request forms and I was

the first to look at the slides. Once I had finished my reporting, Dr Perunovic compared my report to the original report so that I could fill out the summary table as seen in Table 6. I then collated the final report form as seen in Figure 16. I had to be first as I was distributing the slides to the other Consultant BMS and giving them the results and feedback.

Reviews by Consultant BMS

It was expected that the study would take approximately six months, however it was delayed due to workload pressures within the volunteer group plus the long term sickness of one of the BMS, so that it actually took 12 months to complete. Slides from the cases I had reported were packed safely and securely in slide cases together with their request forms and sent to each participant through the post with Royal Mail. Two box slide sets which equated to ten cases at a time were sent to each Consultant BMS and these were tracked on a spreadsheet which was the central register. The central register tracked the dates of who had which cases, when they sent their reports back to me electronically and the date when I received the original paper reports together with the cases back at base. By having a central register, I was able to keep track of where the slides had been and what cases needed to be sent on.

Statistical Analysis

All data sent back from each Consultant BMS was entered on to a Microsoft Excel spreadsheet and statistical analysis was performed using the kappa test (κ). The kappa test is used for 'determining the agreement between two operators or techniques' (Blann, 2015). This calculation also takes in to account the level of agreement that could occur if left to chance.

$$\kappa = \frac{\text{Observed agreement – Chance agreement}}{\text{Maximum agreement – Chance agreement}}$$

$$\kappa = \frac{P_O - P_E}{1 - P_E}$$

This calculation above represents the 'chance-corrected proportional agreement' where

- n = total observed frequency (total number of specimens of which in this case is 157
- O_D = sum of observed frequencies along the diagonal
- E_D = sum of expected frequencies along the diagonal
- $P_O = O_D/n$
- $P_E = E_D/\text{n}$
- 1 in the denominator represents maximum agreement

(Watson and Petrie, 2010)

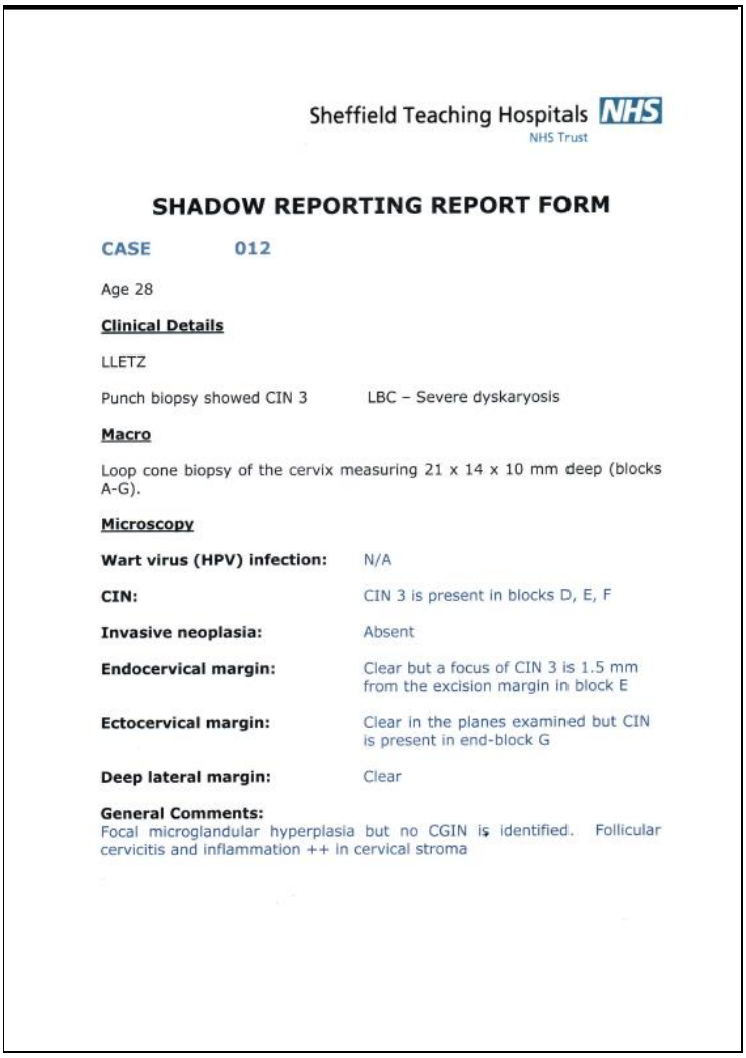
Table 5 The kappa statistic

Value of kappa	Strength of agreement
0 - 2	Poor
0.21 – 0.4	Fair
0.41 – 0.6	Moderate
0.61 – 0.8	Good
0.81 – 1.0	Very good

The kappa test will bring a result back of between 0 to 1 depending on the levels of agreement and disagreement which is detailed in the table above with a kappa value of 1 representing excellent agreement and 0 representing agreement left to chance (Altman and Bland, 1994: Blann, 2015)

In this study, I was comparing the performance of the Consultant BMS against the final report issued by the Histopathologists. The kappa test was applied to the number of agreements and disagreements between the Consultant BMS and Histopathologists.

Figure 16 Shadow Reporting Report Form



Sheffield Teaching Hospitals NHS
NHS Trust

SHADOW REPORTING REPORT FORM

CASE 012

Age 28

Clinical Details

LLETZ

Punch biopsy showed CIN 3 LBC – Severe dyskaryosis

Macro

Loop cone biopsy of the cervix measuring 21 x 14 x 10 mm deep (blocks A-G).

Microscopy

Wart virus (HPV) infection:	N/A
CIN:	CIN 3 is present in blocks D, E, F
Invasive neoplasia:	Absent
Endocervical margin:	Clear but a focus of CIN 3 is 1.5 mm from the excision margin in block E
Ectocervical margin:	Clear in the planes examined but CIN is present in end-block G
Deep lateral margin:	Clear

General Comments:
Focal microglandular hyperplasia but no CGIN is identified. Follicular cervicitis and inflammation ++ in cervical stroma

Results

The total results were collected and tabulated below compared with the with final pathologists report which was set as the gold standard. Each case is labelled 1 to 157 with the final report column showing the report as the disease category as stated in Table 4 e.g. 3 represents CIN 3. Each Consultant BMS is shown by their initials and the shaded boxes represent agreement against the final report.

Table 6 Histopathology grading on LLETZ samples by Consultant BMS

No	Final Report	K	A	N	B	M	P
1	3	3	3	3	3	3	3
2	0	0	1	0	10	7	2
3	3	3	2	3	3	2	2
4	2	2	2	2	3	2	2
5	10	10	10	10	10	10	3
6	3	3	3	8	3	3	3
7	0	0	0	0	0	0	1
8	1	2	2	2	2	1	8
9	3	3	3	3	3	2	3
10	0	0	0	0	2	0	0
11	3	3	8	3	3	3	0
12	3	3	3	3	3	3	3
13	3	3	3	3	3	3	3
14	3	11	3	3	3	3	3
15	0	0	0	0	0	1	0
16	3	3	3	3	3	3	2
17	2	3	2	2	3	2	2
18	3	3	3	3	3	3	3
19	2	3	2	3	3	3	3
20	1	3	1	2	2	2	3
21	11	11	11	11	0	11	0
22	1	3	1	1	3	3	3
23	0	0	0	0	0	0	0

24	0	0	1	0	1	7	2
25	3	3	3	3	3	3	3
26	3	3	3	3	2	3	3
27	1	1	0	0	1	1	0
28	3	3	3	3	3	3	3
29	3	3	3	3	3	3	3
30	3	2	2	3	3	2	2
31	3	3	2	3	3	3	3
32	0	0	0	0	1	0	1
33	0	0	1	0	1	1	0
34	0	1	0	0	3	0	0
35	3	3	3	3	10	3	3
36	3	3	3	3	3	3	3
37	3	3	3	3	3	3	3
38	2	2	2	2	3	2	8
39	3	3	3	3	2	3	3
40	3	8	8	8	3	8	3
41	0	12	0	0	12	0	0
42	3	3	3	3	3	3	3
43	2	2	2	2	3	2	2
44	2	3	3	3	3	3	3
45	2	3	2	2	3	2	2
46	2	2	3	3	3	3	3
47	2	3	3	1	3	8	1
48	3	3	3	3	3	3	1
49	2	0	1	2	2	8	1
50	3	3	3	3	3	3	3
51	0	0	0	0	1	0	0
52	3	3	3	2	3	3	1
53	3	3	3	3	2	3	3
54	0	0	0	0	2	0	0
55	3	3	3	3	11	3	3
56	2	3	2	2	3	2	2
57	0	0	0	0	2	7	1
58	3	3	3	3	3	3	3
59	3	3	3	3	3	3	3
60	2	2	1	4	3	8	0
61	0	0	0	0	13	0	0
62	0	0	0	0	0	0	8
63	3	3	3	3	3	3	3
64	3	0	0	4	8	8	0
65	3	3	3	3	3	3	2
66	3	3	3	3	3	3	3

67	0	1	1	1	2	1	1
68	2	2	1	1	2	1	1
69	3	3	3	3	3	3	2
70	12	12	12	10	12	0	12
71	3	0	0	0	1	0	0
72	0	0	0	0	0	0	0
73	11	3	3	3	3	3	3
74	3	3	3	3	3	3	3
75	2	3	2	3	3	3	1
76	11	11	3	3	12	3	3
77	0	8	0	8	3	1	0
78	3	3	3	3	3	3	3
79	3	3	3	3	3	3	3
80	3	2	3	2	3	2	3
81	0	0	0	0	0	0	0
82	3	3	3	3	3	3	3
83	0	0	0	0	0	0	0
84	3	2	3	3	3	2	1
85	3	3	3	3	3	3	3
86	3	3	3	3	2	3	3
87	3	3	3	3	3	3	3
88	3	3	3	3	3	3	8
89	3	3	3	3	3	3	3
90	0	0	0	0	0	1	0
91	1	0	0	0	1	0	0
92	3	3	3	3	3	3	3
93	3	0	2	3	3	3	3
94	2	2	1	1	2	1	2
95	2	1	1	7	2	1	1
96	2	2	2	7	2	2	0
97	3	3	3	3	3	3	8
98	3	3	3	3	3	3	3
99	3	3	3	3	3	3	3
100	3	3	2	2	1	1	0
101	0	0	0	0	1	0	0
102	3	3	2	3	3	1	0
103	3	3	3	3	3	3	2
104	3	3	3	3	3	3	3
105	3	3	3	3	3	11	3
106	0	0	0	0	0	0	0
107	3	3	3	3	3	3	3
108	1	0	0	0	1	0	0
109	11	3	3	3	3	3	3

110	3	3	3	3	3	3	3
111	3	2	2	3	3	2	2
112	3	8	0	8	2	1	0
113	3	2	1	2	3	1	0
114	3	1	3	3	3	3	3
115	2	3	3	3	3	2	2
116	3	3	3	3	3	2	3
117	3	3	3	3	3	3	3
118	3	3	3	3	3	3	3
119	3	3	3	3	11	3	3
120	3	3	3	3	3	3	8
121	3	0	0	0	0	0	0
122	10	3	10	10	10	10	3
123	1	7	3	0	1	2	2
124	0	7	0	0	0	0	2
125	3	3	2	2	3	8	2
126	3	3	3	3	3	3	2
127	3	3	3	3	3	3	3
128	11	11	3	3	3	11	3
129	0	0	2	1	3	3	2
130	2	8	0	0	2	8	2
131	3	3	2	3	3	3	3
132	1	1	1	1	3	1	2
133	3	3	3	3	3	3	3
134	3	3	3	3	3	3	3
135	2	2	2	2	2	2	2
136	3	0	0	3	0	2	0
137	3	3	3	3	3	3	2
138	3	8	0	8	3	3	2
139	3	11	3	3	3	3	3
140	3	3	3	3	3	3	3
141	3	3	3	3	3	3	3
142	3	3	3	3	3	3	3
143	11	11	11	3	3	3	3
144	3	3	2	2	3	3	2
145	3	3	3	3	3	3	3
146	3	3	3	3	3	3	3
147	3	3	3	3	3	3	2
148	3	3	3	3	3	3	3
149	12	12	12	12	8	3	12
150	11	11	2	11	3	3	2
151	3	3	3	3	3	3	3
152	2	3	3	3	3	3	3

153	3	3	3	3	3	3	3
154	3	3	3	3	3	3	3
155	3	3	3	1	3	3	3
156	0	0	0	0	0	0	0
157	12	12	12	12	12	12	0

Table 7 Final Histological Outcome of 157 cases

Grade of Disease	Number of Cases	Percentage
No CIN (0)	26	16.6%
CIN 1 (1)	8	5.1%
CIN 2 (2)	21	13.4%
CIN 3 (3)	90	57.3%
High grade CIN/CGIN (10)	2	1.3%
Squamous carcinoma of cervix (11)	7	4.5%
Stratified mucin-producing intraepithelial lesion (SMILE) (12)	3	1.9%

Table 8 Comparison of annual reporting rates in England and STHFT (2017/18)

Grade of disease	England %*	STH Numbers	STH %
Inadequate	0.2	0	0
Negative	14.3	56	11.3
CIN 1	12.1	28	5.6
CIN 2	24.9	18	3.6
CIN 3	43.7	336	67.7
CGIN	2.7	4	0.8
Cancer	2.0	54	10.9

*Please note on the national returns HPV/cervicitis (Source KC65 Part E, NHS Digital) have been recorded but for this purpose they have been included as negative (NHS Digital, 2018).

The figures in Table 7 for cervical cancer percentages are lower than in Table 8 as they were for 2010/11 rather than 2017/18. This can be explained as regional cancer centres were starting to be established and would explain the differences between the cancer reporting rates for England compared to STHFT in Table 8. There are higher rates at STHFT which I believe are due to this site being designated as a regional cancer referral centre. This means that the local general hospitals should refer any women with suspected gynaecological cancers to their regional specialist centres for surgery, hence their histology will be reported on these sites explaining the higher rates of cancer that are reported.

Table 9 Summary of Reporting Grades

Code	Final	K	A	N	B	M	P
0	26	29	31	30	14	22	33
1	8	6	13	8	11	15	12
2	21	15	23	16	18	19	29
3	90	88	81	87	101	85	75
4				2			
5							
6							
7		2		2		3	
8		5	2	5	2	7	6
9							
10	2	1	2	3	4	2	
11	7	7	2	2	2	3	
12	3	4	3	2	4	1	2
13					1		
Total	157	157	157	157	157	157	157

Results Analysis

Looking at the specimens separately before statistically analysing them, there was a variation in the reporting as you would expect. There were 26 specimens that were reported as having no CIN (O) but the range reported by the Consultant BMS was 14 to 33. There were eight cases reported as CIN 1 (1 and 7) and the Consultant BMS reporting numbers varied from between 8 to 18. Overall for specimens classified as CIN 2 (2, 4, 5 and 8) there were 21 reported with the Consultant

BMS range from 20 to 35 cases. There were 95 cases reported as high grade CIN and CGIN (3, 9, 10, 12 and 13) with the range for the Consultant BMS between 86 to 110 cases. There were seven cancers with the Consultant BMS reporting from seven to none of them.

Two Consultant BMS missed the same cervical cancer case and reported it negative. This case was reported as FIGO stage 1A1 with a small area of micro-invasion. It must be noted that the previous cervical biopsy was reported as suspicious of cervical cancer and the subsequent LLETZ if reported as negative would have been checked by another colleague. This would be because there was a significant discrepancy between the two reports from the same patient and would not have been missed in a 'real life' setting. All other cervical cancers were either correctly identified or reported as high grade.

In Table 9, there is a greater variation of the reporting grades from 0 to 13 between the Consultant BMS and the Histopathologists. None of the Histopathologists reported the histology as described in Table 4 represented by the numbers 4, 5, 6, 7 and 8 which covered equivocal, probable or ungradeable categories. I believe this is due to the fact that the Histopathologists are very experienced and are used to diagnosing specific lesions. This may have been further helped by the Histopathologists using immunocytochemistry such as p16 to help identify whether a lesion was high grade CIN or not, or requesting further levels to help with their decision making. These extra interventions were not available to the

Consultant BMS to grade and may explain why they reported more samples as equivocal or probable plus they were far less experienced than the Histopathologists.

In this series of LLETZ samples, there were no samples that only had CGIN (9) reported by the Gynae Histopathologists. There were two LLETZ that were reported with co-existing CGIN and CIN.

The following tables show initial overall agreement of all the positive and negative reports of all the Consultant BMS with their initials compared with the final results of the pathologists labelled as Path.

Tables 10 (K, A, N, B, M and P) Total positive and negative agreements

K	K - Positive	K- Negative	Total
Path - Positive	123	8	131
Path - Negative	5	21	26
Total	128	29	157

Percentage agreement = 91.7% κ = 0.714

A	A - Positive	A - Negative	Total
Path - Positive	121	10	131
Path - Negative	5	21	26
Total	126	31	157

Percentage agreement = 90.4% κ = 0.679

N	N - Positive	N - Negative	Total
Path - Positive	124	7	131
Path - Negative	3	23	26
Total	127	30	157

Percentage agreement = 93.6% κ = 0.783

B	B - Positive	B - Negative	Total
Path - Positive	128	3	131
Path - Negative	15	11	26
Total	143	14	157

Percentage agreement = 88.5% κ = 0.491

M	M - Positive	M - Negative	Total
Path - Positive	126	5	131
Path - Negative	9	17	26
Total	135	22	157

Percentage agreement = 91.1% κ = 0.656

P	P - Positive	P - Negative	Total
Path - Positive	115	16	131
Path - Negative	9	17	26
Total	124	33	157

Percentage agreement = 84.1% κ = 0.480

The overall agreement between the Consultant BMS and the final Histopathologist report for negative and positive results was classed as very good with the kappa test but this was a very simplistic view of overall inter-observer agreement and disagreement i.e. positive versus negative report without taking into account the different reporting categories. The overall percentage of agreement ranges from 93.6% to 84.1%

and the inter-observer agreement with kappa ranged from 0.783 to 0.480. Four of the Consultant BMS had an inter-observer agreement of good and the remaining two were classed as moderate. The value of kappa is reliant on the number of categories and the fewer categories that there are tends to result in a higher kappa result which can be seen from the results above in Tables 9 (Watson and Petrie, 2010).

Agreement between Negative, low grade CIN and high grade CIN +

The following tables look at the agreement and disagreement rates broken down in to the classifications of negative, low grade CIN and high grade lesions including glandular neoplasia and cancer of each of the Consultant BMS reports compared to the final pathologists' report using the kappa test. This correlates with how a colposcopist would manage their patient on a two tier system of reporting and follows The Bethesda System (TBS) of reporting (Nayar and Wilbur, 2014). Reporting categories were grouped together as the following to facilitate the kappa analysis.

- No CIN = 0
- Low grade (LG) = CIN 1 (1) and probably low grade CIN (7)
- High grade (HG) = CIN 2 (2), ungradeable CIN (4), equivocal CIN (5), probably high grade CIN (8), CIN 3 (3), CGIN (9), high grade CIN/CGIN (10), stratified

mucin-producing intraepithelial lesion (SMILE) (12), low grade CIN/CGIN (13) and cancer (11)

Tables 11 (K, A, N, B, M and P) Negative, low grade CIN and high grade CIN +

		Consultant BMS K			
	Grade	No CIN	LG	HG	Total
Path	No CIN	21	3	2	26
	LG	2	3	3	8
	HG	6	2	115	123
	Total	29	8	120	157

Percentage agreement = 88.5% κ = 0.689 (.95 CI 0.533 to 0.824)

		Consultant BMS A			
	Grade	No CIN	LG	HG	Total
Path	No CIN	21	4	1	26
	LG	3	3	2	8
	HG	7	6	110	123
	Total	31	13	113	157

Percentage agreement = 88.5% κ = 0.633 (.95 CI 0.494 to 0.772)

		Consultant BMS N			
	Grade	No CIN	LG	HG	Total
Path	No CIN	23	2	1	26
	LG	4	2	2	8
	HG	3	6	114	123
	Total	30	10	117	157

Percentage agreement = 85.4% κ = 0.699 (.95 CI 0.569 to 0.830)

		Consultant BMS B			
	Grade	No CIN	LG	HG	Total
Path	No CIN	11	5	10	26
	LG	0	4	4	8
	HG	3	2	118	123
	Total	14	11	132	157

Percentage agreement = 84.7% κ = 0.527 (.95 CI 0.352 to 0.701)

		Consultant BMS M			
	Grade	No CIN	LG	HG	Total
Path	No CIN	17	8	1	26
	LG	2	3	3	8
	HG	3	7	113	123
	Total	22	18	117	157

Percentage agreement = 84.7% κ = 0.605 (.95 CI 0.460 to 0.751)

		Consultant BMS P			
	Grade	No CIN	LG	HG	Total
Path	No CIN	17	4	5	26
	LG	3	0	5	8
	HG	13	8	102	123
	Total	33	12	112	157

Percentage agreement = 75.8% κ = 0.398 (.95 CI 0.232 to 0.565)

The overall percentage of agreement ranges from 88.5% to 75.8% and the inter-observer agreement with kappa ranged from 0.699 to 0.398. Four of the Consultant BMS had an inter-observer agreement of good, one had moderate and the remaining Consultant BMS was classified as fair.

Agreement between Negative, CIN 1, CIN2, CIN 3 with CGIN and Cancer Reports

The following tables look at the agreement and disagreement rates broken down in to the classifications of negative, CIN including precancerous lesions of glandular neoplasia and cancer of each of the Consultant BMS reports compared to the final pathologists' report using the kappa test.

Reporting categories were grouped together as the following to facilitate the kappa analysis

- No CIN = 0
- CIN 1 = CIN 1 (1) and probably low grade CIN (7)
- CIN 2 = CIN 2 (2), ungradeable CIN (4), equivocal CIN (5) and probably high grade CIN (8)
- CIN 3 = CIN 3 (3), CGIN (9), high grade CIN/CGIN (10), stratified mucin-producing intraepithelial lesion (SMILE) (12) and low grade CIN/CGIN (13)
- Cancer = cancer (11)

Tables 12 (K, A, N, B, M and P) Negative, CIN 1, CIN2, CIN 3 and Cancer

		Consultant BMS K					
		No CIN	CIN 1	CIN 2	CIN 3	Cancer	Total
Pathologist	No CIN (0)	21	3	1	1	0	26
	CIN 1 (1,7)	2	3	1	2	0	8
	CIN 2 (2,4,5,8)	1	1	10	9	0	21
	CIN 3 (3,9,10,12,13)	5	1	8	79	2	95
	Cancer (11)	0	0	0	2	5	7
	Total	29	8	20	93	7	157

Percentage agreement = 75.2% κ = 0.579 (.95 CI 0.464 to 0.693)

		Consultant BMS A					
		No CIN	CIN 1	CIN 2	CIN 3	Cancer	Total
Pathologist	No CIN (0)	21	4	1	0	0	26
	CIN 1 (1,7)	3	3	1	1	0	8
	CIN 2 (2,4,5,8)	1	5	10	5	0	21
	CIN 3 (3,9,10,12,13)	6	1	12	76	0	95
	Cancer (11)	0	0	1	4	2	7
	Total	31	13	25	86	2	157

Percentage agreement = 71.3% κ = 0.530 (.95 CI 0.414 to 0.646)

		Consultant BMS N					
		No CIN	CIN 1	CIN 2	CIN 3	Cancer	Total
Pathologist	No CIN (0)	23	2	1	0	0	26
	CIN 1 (1,7)	4	2	2	0	0	8
	CIN 2 (2,4,5,8)	1	5	9	6	0	21
	CIN 3 (3,9,10,12,13)	2	1	11	81	0	95
	Cancer (11)	0	0	0	5	2	7
	Total	30	10	23	92	2	157

Percentage agreement = 74.5% κ = 0.568 (.95 CI 0.453 to 0.684)

		Consultant BMS B					
		No CIN	CIN 1	CIN 2	CIN 3	Cancer	Total
Pathologist	No CIN (0)	11	5	4	6	0	26
	CIN 1 (1,7)	0	4	2	2	0	8
	CIN 2 (2,4,5,8)	0	0	7	14	0	21
	CIN 3 (3,9,10,12,13)	2	2	7	82	2	95
	Cancer (11)	1	0	0	6	0	7
	Total	14	11	20	110	2	157

Percentage agreement = 66.2% κ = 0.375 (.95 CI 0.238 to 0.512)

		Consultant BMS M					
		No CIN	CIN 1	CIN 2	CIN 3	Cancer	Total
Pathologist	No CIN (0)	17	8	0	1	0	26
	CIN 1 (1,7)	2	3	2	1	0	8
	CIN 2 (2,4,5,8)	0	3	13	5	0	21
	CIN 3 (3,9,10,12,13)	3	4	11	76	1	95
	Cancer (11)	0	0	0	5	2	7
	Total	22	18	26	88	3	157

Percentage agreement = 70.7% κ = 0.519 (.95 CI 0.402 to 0.636)

		Consultant BMS P					
		No CIN	CIN 1	CIN 2	CIN 3	Cancer	Total
Pathologist	No CIN (0)	17	4	5	0	0	26
	CIN 1 (1,7)	3	0	2	3	0	8
	CIN 2 (2,4,5,8)	2	5	10	4	0	21
	CIN 3 (3,9,10,12,13)	10	3	16	66	0	95
	Cancer (11)	1	0	1	5	0	7
	Total	33	12	34	78	0	157

Percentage agreement = 59.2% κ = 0.355 (.95 CI 0.233 to 0.476)

The overall percentage of agreement ranges from 75.2% to 59.2% and the inter-observer agreement with kappa ranged from 0.579 to 0.355. The inter-observer agreement was

classified as moderate for four of the Consultant BMS and the rest were fair.

Agreement between Negative, CIN 1, CIN2, CIN 3, glandular neoplasia and Cancer Reports

The following tables look at the agreement and disagreement rates broken down in to the classifications of negative, CIN, glandular neoplasia and cancer of each of the Consultant BMS reports compared to the final pathologists' report using the kappa test.

Reporting categories were grouped together as the following to facilitate the kappa analysis

- No CIN = 0
- CIN 1 = CIN 1 (1) and probably low grade CIN (7)
- CIN 2 = CIN 2 (2), ungradeable CIN (4), equivocal CIN (5) and probably high grade CIN (8)
- CIN 3 = CIN 3 (3)
- Glandular neoplasia (GN) = CGIN (9), high grade CIN/CGIN (10), stratified mucin-producing intraepithelial lesion (SMILE) (12) and low grade CIN/CGIN (13)
- Cancer = cancer (11)

Tables 13 (K, A, N, B, M and P) Negative, CIN 1, CIN2, CIN 3, GN and Cancer

		Consultant BMS K						
Pathologist		No CIN	CIN 1	CIN 2	CIN 3	GN	Cancer	Total
	No CIN	21	3	1	0	1	0	26
	CIN 1	2	3	1	2	0	0	8
	CIN 2	1	1	10	9	0	0	21
	CIN 3	5	1	8	74	0	2	90
	GN	0	0	0	1	4	0	5
	Cancer	0	0	0	2	0	5	7
	Total	29	8	20	88	5	7	157

Percentage agreement = 74.5% κ = 0.593 (.95 CI 0.484 to 0.702)

		Consultant BMS A						
Pathologist		No CIN	CIN 1	CIN 2	CIN 3	GN	Cancer	Total
	No CIN	21	4	1	0	0	0	26
	CIN 1	3	3	1	1	0	0	8
	CIN 2	1	5	10	5	0	0	21
	CIN 3	6	1	12	71	0	0	90
	GN	0	0	0	0	5	0	5
	Cancer	0	0	1	4	0	2	7
	Total	31	13	25	81	5	2	157

Percentage agreement = 71.3% κ = 0.555 (.95 CI 0.445 to 0.665)

		Consultant BMS N						
Pathologist		No CIN	CIN 1	CIN 2	CIN 3	GN	Cancer	Total
	No CIN	23	2	1	0	0	0	26
	CIN 1	4	2	2	0	0	0	8
	CIN 2	1	5	9	6	0	0	21
	CIN 3	2	1	11	76	0	0	90
	GN	0	0	0	0	5	0	5
	Cancer	0	0	0	5	0	2	7
	Total	30	10	23	87	5	2	157

Percentage agreement = 74.5% κ = 0.593 (.95 CI 0.484 to 0.702)

		Consultant BMS B						
Pathologist		No CIN	CIN 1	CIN 2	CIN 3	GN	Cancer	Total
	No CIN	11	5	4	3	3	0	26
	CIN 1	0	4	2	2	0	0	8
	CIN 2	0	0	7	14	0	0	21
	CIN 3	2	2	6	77	1	2	90
	GN	0	0	1	0	4	0	5
	Cancer	1	0	0	5	0	1	7
	Total	14	11	20	101	8	3	157

Percentage agreement = 66.2% κ = 0.431 (.95 CI 0.306 to 0.556)

		Consultant BMS M						
Pathologist		No CIN	CIN 1	CIN 2	CIN 3	GN	Cancer	Total
	No CIN	17	8	0	1	0	0	26
	CIN 1	2	3	2	1	0	0	8
	CIN 2	0	3	13	5	0	0	21
	CIN 3	5	1	8	74	0	2	90
	GN	1	0	0	1	3	0	5
	Cancer	0	0	0	5	0	2	7
	Total	25	15	23	87	3	4	157

Percentage agreement = 70.1% κ = 0.545 (.95 CI 0.433 to 0.657)

		Consultant BMS P						
Pathologist		No CIN	CIN 1	CIN 2	CIN 3	GN	Cancer	Total
	No CIN	17	4	5	0	0	0	26
	CIN 1	3	0	3	2	0	0	8
	CIN 2	2	5	10	4	0	0	21
	CIN 3	9	3	16	62	0	0	90
	GN	1	0	0	2	2	0	5
	Cancer	1	0	1	5	0	0	7
	Total	33	12	35	75	2	0	157

Percentage agreement = 58.0% κ = 0.360 (.95 CI 0.243 to 0.478)

The overall percentage of agreement ranges from 74.5% to 58.0% and the inter-observer agreement with kappa ranged from 0.593 to 0.360. There was an increased inter-observer

agreement even though there were more categories demonstrating that there was more agreement with the reporting categories which is not what you would expect with more options (Watson and Petrie, 2010). The inter-observer agreement was classified as moderate for five of the Consultant BMS and the final Consultant BMS was classified as fair.

Margins

On a LLETZ sample, there are three margins that need to be considered to report whether the lesion has been fully excised and these have been described previously (Figure 9).

Tables 14 (K, A, N, B, M and P) Excisional margins

		Consultant BMS K					
	Margin	Endocervical		Ectocervical		Deep lateral margin	
		Pos	Neg	Pos	Neg	Pos	Neg
Path	Pos	12	2	31	12	0	1
	Neg	16	127	21	93	3	153
	Total	28	129	52	105	3	154

Endocervical margins – percentage agreement = 88.5% κ = 0.514

Ectocervical margins - percentage agreement = 79.0% κ = 0.504

Deep lateral margins - percentage agreement = 97.5%*

		Consultant BMS A					
	Margin	Endocervical		Ectocervical		Deep lateral margin	
		Pos	Neg	Pos	Neg	Pos	Neg
Path	Pos	9	5	33	10	1	0
	Neg	11	132	22	92	4	152
	Total	20	137	55	102	5	152

Endocervical margins – percentage agreement = 89.8% κ = 0.474

Ectocervical margins - percentage agreement = 79.6% κ = 0.529

Deep lateral margins - percentage agreement = 97.5% κ = 0.326

		Consultant BMS N					
	Margin	Endocervical		Ectocervical		Deep lateral margin	
		Pos	Neg	Pos	Neg	Pos	Neg
Path	Pos	11	3	28	15	0	1
	Neg	6	137	5	109	2	154
	Total	17	140	33	124	2	155

Endocervical margins – percentage agreement = 94.3% κ = 0.678

Ectocervical margins - percentage agreement = 87.3% κ = 0.655

Deep lateral margins - percentage agreement = 98.1%*

		Consultant BMS B					
	Margin	Endocervical		Ectocervical		Deep lateral margin	
		Pos	Neg	Pos	Neg	Pos	Neg
Path	Pos	10	4	23	20	0	1
	Neg	16	127	6	108	3	153
	Total	26	131	29	128	3	154

Endocervical margins – percentage agreement = 87.3% κ = 0.434

Ectocervical margins - percentage agreement = 83.4% κ = 0.537

Deep lateral margins - percentage agreement = 97.5%*

		Consultant BMS M					
	Margin	Endocervical		Ectocervical		Deep lateral margin	
		Pos	Neg	Pos	Neg	Pos	Neg
Path	Pos	9	5	29	14	1	0
	Neg	16	127	13	101	5	151
	Total	25	132	42	115	6	151

Endocervical margins – percentage agreement = 86.6% κ = 0.392

Ectocervical margins - percentage agreement = 82.8% κ = 0.565

Deep lateral margins - percentage agreement = 96.8% κ = 0.278

		Consultant BMS P					
	Margin	Endocervical		Ectocervical		Deep lateral margin	
		Pos	Neg	Pos	Neg	Pos	Neg
Path	Pos	6	8	21	22	0	1
	Neg	6	137	8	106	2	154
	Total	12	145	29	128	2	155

Endocervical margins – percentage agreement = 91.1% κ = 0.413

Ectocervical margins - percentage agreement = 80.9% κ = 0.465

Deep lateral margins - percentage agreement = 98.1%*

*No kappa could be calculated as this data has an observed concordance which is smaller than mean-chance.

Overall there were 14 cases that were positive at the endocervical margins and the ranges reported from the Consultant BMS were between 12 to 6 cases. The overall percentage of agreement ranged from 87.3% to 79.0% with the inter-observer agreement with kappa ranged from 0.678 to 0.392. The high percentage of agreement is probably due to the fact that most of the margins were negative.

There were 43 cases reported as having disease involved with the ectocervical margins and the ranges reported from the Consultant BMS were between 33 to 21 cases. The overall percentage of agreement ranged from 94.3% to 86.6% with the inter-observer agreement with kappa ranged from 0.655 to 0.465. One Consultant BMS had good agreement with the other five Consultant BMS having moderate agreement.

There was only one case where the deep lateral margins were positive with the rest being negative, therefore a meaningful conclusion could not be made.

Histological evidence of Human Papillomavirus (HPV) infection

The following tables demonstrate the agreement between the pathologists and the Consultant BMS regarding the presence of HPV histologically or not in the LLETZ specimens.

Tables 15 (K, A, N, B, M and P) Evidence of HPV infection

		Consultant BMS K		
	HPV	Pos	Neg	Total
Path	Pos	106	6	112
	Neg	24	21	45
	Total	130	27	157

HPV – percentage agreement = 80.9% κ = 0.469

		Consultant BMS A		
	HPV	Pos	Neg	Total
Path	Pos	68	44	112
	Neg	20	25	45
	Total	88	69	147

HPV – percentage agreement = 59.2% κ = 0.140

		Consultant BMS N		
	HPV	Pos	Neg	Total
Path	Pos	86	26	112
	Neg	16	29	45
	Total	102	55	157

HPV – percentage agreement = 73.2% κ = 0.387

		Consultant BMS B		
	HPV	Pos	Neg	Total
Path	Pos	73	39	112
	Neg	12	33	45
	Total	85	72	157

HPV – percentage agreement = 67.5% κ = 0.327

		Consultant BMS M		
	HPV	Pos	Neg	Total
Path	Pos	96	16	112
	Neg	29	16	45
	Total	125	32	157

HPV – percentage agreement = 71.3% κ = 0.233

		Consultant BMS P		
	HPV	Pos	Neg	Total
Path	Pos	93	19	112
	Neg	23	22	45
	Total	116	41	157

HPV – percentage agreement = 73.2% κ = 0.328

There were 112 samples that were reported with histological evidence of HPV infection. The Consultant BMS agreement ranged from 80.9% to 59.2% with the kappa agreement from 0.469 to 0.140. One Consultant BMS demonstrated moderate agreement, four with fair agreement and one Consultant BMS had poor agreement.

Discussion of Results

Overall on the initial interpretation of the results, there would appear to be good inter-observer agreement between the Histopathologists final reports and the reports of the Consultant BMS as seen in Table 6 with most categories being rated as good agreement using the kappa classification. This is at least as good and if not better than the Histopathologists' performance in the literature searches. Even when there were more reporting categories, the level of concordance was still moderate with the kappa classification. This demonstrated that the Consultant BMS were able to identify the different

categories of CIN, CGIN and cancer with a moderate level of agreement.

The inter-observer agreement from the original pilot site of two Consultant BMS of good was demonstrated in the larger study of Consultant BMS from the UK which was good and moderate agreement using the kappa coefficient. The correlation was good despite there being many options of reporting categories to choose from which should have been restricted to more accurately reflect the recommended RCPath minimum data sets. The extra reporting categories such as equivocal CIN, possibly low grade CIN and possibly high grade CIN were included to cover every possible reporting option for the Consultant BMS.

The histological features associated with CIN are well-described in text books and journals but the assessment is still subjective due to the continuous spectrum of the development of CIN through to cancer in the epithelium. It is well-documented that there is extensive inter-observer variation of Histopathologists when it comes to classifying CIN and the interpretation of CIN 1 in particular is poorly reproducible (Parker et al, 2002: Ismail et al, 1989: Creagh et al, 1995: Stoler et al, 2001: McCluggage et al, 1998: de Vet et al, 1990). The disagreement at the lower grades of CIN is due to the interpretation of koilocytes associated with an HPV infection which exaggerates the nuclear atypia. There tends to be higher agreement with the diagnosis of no CIN and CIN 3 (Robertson et al, 1989). In this paper, the overall agreement

was κ = 0.34 which is classified as fair whereas looking at the same reporting categories, the overall agreement of the Consultant BMS was κ = 0.592 which is classified as moderate agreement. There was still low agreement on whether histological features of HPV was present with a κ = 0.21. Our overall agreement with features of HPV was κ = 0.314 so was comparable to experienced Histopathologists.

On all the papers that were found where inter-observer variation was calculated, it was found to be fair only, which increased to moderate agreement if a two-tiered system of classification was used as in The Bethesda system (McCluggage et al, 1998). Most of the papers reviewed were based on the interpretation of cervical biopsies rather than LLETZ specimens but the interpretation of CIN in all cervical histology sections follows the same classification guidelines that have been described previously. As the papers were based on the diagnosis of cervical biopsies, the margins are not relevant so I was unable to determine how the Consultant BMS compared to the Histopathologists. It was reassuring to find that my findings were comparable to the published data and the inter-observer agreements were consistent with the findings in my original pilot study.

Consultant BMS B tended to overcall which probably reflected that he had the least histological experience of all the Consultant BMS that participated in this study.

Consultant BMS P had the lowest agreement compared to the rest of the Consultant BMS. Although she came from a histology background, she was the least experienced Consultant BMS having only just passed the ASD plus she did not attend any of the training sessions.

This would suggest that the training programme was an integral part of the study. If such a training programme is taken forward, a training course covering the basics and 'pitfalls' of reporting cervical samples should be a mandatory part of the programme. Such a course provides the background, knowledge and a more equitable starting point for all the BMS going forward. The self-assessment stage should be more formalised to aid with the development of bespoke training plans for future BMS undertaking the reporting of NHSCSP samples if a modular programme was developed.

Consultant BMS B and P both missed the cervical cancer FIGO stage 1A1. This case had a previous diagnostic biopsy which was diagnosed with cervical cancer and colposcopically presented as cancer. In real practice such cases would be reviewed with a colleague and would be discussed at the Gynae cancer MDT.

Where there were discrepant findings, the Consultant BMS paper reports were looked at more closely to see if they had difficulties with the diagnosis and what these were likely to be. As expected, the areas of concern were the typical pitfalls in

reporting cervical pathology such as when the epithelium was thin in atrophic cases, sections cross-cut so there was not the full thickness of epithelium, reactive and reparative changes and metaplastic squamous epithelium. In real practice, such cases would be discussed with colleagues and extra tests would be requested such as immunocytochemical tests e.g. p16 to help with the diagnosis (NHS Cervical Screening Programme, 2012).

Discrepancies in whether the margins were involved in cervical disease or not, were due to difficulties in interpreting tissue with diathermy artefact and where there were crypts with CIN close to the endocervical and deep lateral margins. Again extra tests such a p16 and reviewing with colleagues would help in the diagnosis and this is the practice that would normally happen. The NHSCSP has introduced HPV testing to assess test of cure (TOC) following the treatment by LLETZ and this has been found to be more sensitive for detecting residual disease or recurrence than cytology alone (Public Health England, 2016) .

These pitfalls cause the same diagnostic difficulties for experienced Histopathologists and the same found with trainee pathologists. It must be remembered that the Consultant BMS in this study were practicing independently and did not have access to any further tests or opinions. They had to make a decision on the sections in front of them and they were possibly concentrating on getting the grade of intraepithelial

neoplasia right devoting less attention to the other clinically important parameters which is an indicator of inexperience.

There was less agreement on the histological presence of HPV between the Consultant BMS and Gynae Histopathologists. This is in line with documented evidence of Consultant Histopathologists having little agreement between themselves as to whether histological features of HPV are present or not (Parker et al, 2002: Ismail et al, 1989: Creagh et al, 1995: Stoler et al, 2001: McCluggage et al, 1998: de Vet et al, 1990). This is because the features associated with HPV histologically are koilocytes and their interpretation is quite subjective as the criteria for diagnosis is not as clearly defined as for CIN.

Discussion

LLETZ Reporting

Essentially this study was to explore the possibilities of fast-tracking Consultant BMS through to reporting selected specimens such as LLETZ to help with workloads in histopathology laboratories and to see if the results from the original pilot in 2010 could be replicated around the UK. LLETZ specimens were chosen as they are clinically low risk as in the majority of cases there is a prior diagnosis, there is a lot of material to examine and they form a substantial part of the workload for a Gynae Histopathologist. In my own laboratory we get approximately 500 LLETZ specimens a year. It is acknowledged that the Consultant BMS reports were compared to the final reports of one of four Gynae Histopathologists rather than a consensus opinion which would have made the data more robust. However, I felt this was negated by the fact that the STHFT Histopathologists were highly specialised in gynaecological pathology with extensive experience and they frequently review each other's work as part of the work up for Gynae cancer MDTs, hence their reporting is remarkably consistent. It is extremely rare for there to be any changes of opinion.

As the LLETZ specimens were sequential and not preselected, they should reflect the workload in real practice. As can be seen in Tables 7 and 8, STHFT tends to have more cases reported as CIN 2 + with 83% in 2018/18 compared to the

figures for England of 73.3% and in this study of 78.4%. Our high grade rates may be higher due to practicing conservative management of women with CIN 2 and having a prior diagnostic cervical biopsy. As stated earlier, STHFT is a cancer referral centre and could be another explanation for the higher rates. The study had 78.4% reported as CIN 2 + which reflects a true and comparable workload as seen in England.

On the thorough examination of the different reporting categories (Table 10 to 15), there was good agreement between the Consultant BMS and the final report that was generated as the 'gold' standard for correlation. The concordance was good despite all the Consultant BMS reporting independently which would not happen in real practice as any discrepant findings or mismatches would be discussed with colleagues or extra tests would be requested to aid diagnosis.

The analysis demonstrates that an experienced BMS could undertake the reporting of LLETZ specimens with minimal training, however it must be noted that the six Consultant BMS that participated in this preliminary study had substantial experience in their roles of reporting cervical cytology, however they had different histological experience which could explain some of the differences in their overall agreement. For any future programmes, I would suggest that there was a more formal assessment prior to starting the training and with on-going assessment to gauge progress and to tailor any training plans moving forward. In general, the overall

agreement was consistent from my original pilot study and carried across to the larger study. I believe this demonstrates that there is potential to train this group of experienced BMS and 'fast-track' them through to reporting selected cases.

Possibly an area of the study that could have been further explored would be the intra-observer variability of the individual Consultant BMS. As the interpretation of histology and cytology is subjective, opinions can change on the same slides if they are presented to you at a different time. This is known as intra-observer variability (McCluggage et al, 1998 and Robertson et al, 1989). If this study was repeated, I would suggest that 10% of cases would be recirculated for reporting to assess the consistency of reporting not only between the Consultant BMS but for them individually. The results of the recirculated cases would be compared to rates found in the literature. This would provide further evidence to say whether or not Consultant BMS reporting was at least equitable to Consultant Histopathologists and provide evidence on consistency. If found to be comparable and consistency demonstrated, this would strengthen the evidence to suggest that Consultant BMS with suitable experience and competency could be 'fast-tracked' to report LLETZ. I would also include the Gynae Histopathologists as part of this exercise to corroborate my assumption about the consistency of their reporting.

Proposal to the Conjoint Board

To move this study forward, the report will be sent to the conjoint board of the RCPath and the IBMS. The board should look at developing a training programme to look at the modular reporting of selected specimens such as LLETZ specimens with the possibility of expanding the remit to cover all specimens from the cervix. As stated earlier, LLETZ specimens are part of the treatment regime and classified as clinically low risk as there is already an existing diagnosis in the majority of cases. LLETZ samples are the best specimens to start to develop reporting skills as there is a large amount of material to examine and will enable the BMS to build their confidence. As my study shows, a Consultant BMS can report these cases with reasonable accuracy after minimal training. As their confidence grows, other specimens can be introduced such as cervical biopsies and polyps. LLETZ specimens and cervical biopsies are part of the NHSCSP with agreed national targets for their turnaround times (TATs). These specimens would be suitable cases for qualified Consultant BMS to focus their reporting as they are time-sensitive.

I would suggest that the training programme follows the template of the ASD programme for Histopathology reporting. An initial interview should take place to assess the suitability of the prospective BMS. As part of this interview, there should be a more formal assessment with a questionnaire and slide test to gauge their experience and their commitment to the training programme. There would be an agreed number of

cases to be reported and recorded in a portfolio with their supervising Histopathologist. By completing a portfolio any training issues would be identified such as reporting CIN at the margins or grading problems. The BMS should perform audits comparing their findings to the final report and the colposcopic impression. They should write up interesting cases as part of their portfolio presentation discussing how the use of immunocytochemical tests helped them make the final diagnosis. During their training, they would be expected to attend the Colposcopy MDTs and present the histology for the cervical specimens under the supervision of their named Histopathologist. These meetings and presentations would be recorded in their portfolio. The portfolio would be sent to the RCPath and IBMS Conjoint Board for assessment and if the portfolio passed this stage there would be an exit examination which would demonstrate that the BMS had reached the necessary standard to proceed with the next stage of reporting – equivalent to stage D. This final stage would be the consolidation period where the BMS would start to report independently. During this probationary period, the supervising Histopathologist would review a selection of cases until they were confident that the BMS was deemed competent to report independently.

I would anticipate that this module should take a year to complete but would depend on their previous experience. Other modules could be developed or expanded to cover

different areas of gynaecological pathology such as reporting benign hysterectomy specimens and endometrial samples.

This training programme should be more achievable and acceptable to the BMS going through the process rather than the four years at least, associated with the current ASD for Histopathology reporting. This should provide more timely benefits to Trusts that are struggling with the recruitment of Histopathologists and allows the Histopathologists to focus on the more complex cases. BMS going through this process should still have protected time however this would still be less of a burden on departments when compared to the commitment associated with the full ASD Gynaecological Histopathology reporting programme. There are only a few BMS that have successfully completed the ASD and as stated earlier, there is a high dropout rate probably due to the time commitment of a minimum of four years and the lack of protected time. There was a dropout rate of a third in this study reiterating that any prospective BMS must have the time and commitment to complete the programme. I believe that if this reporting post was introduced, it would need to be properly resourced with protected time, workplace support and appropriate grading.

External Quality Assurance (EQA) Scheme

The NHSCSP sets performance standards for all the reporting aspects of the programme. There are national returns called KC61 for cervical cytology and KC65 for colposcopy which sets

the key performance indicators (KPIs). Such standards measure TATs, reporting profiles and minimum numbers cytologists should screen/report or new women colposcopy clinicians should see. As part of these performance standards, cervical cytology has a dedicated external quality assurance (EQA) scheme where slides are distributed to test everybody who screens and reports slides for the NHSCSP. If any slides are missed, there is a poor performance protocol that gives the manager guidance on methods to monitor improvement and information on any remedial training if required.

There is currently no EQA scheme for histology specimens as part of the NHSCSP although there are guidelines as to how to report these for the programme (NHS Cervical Screening Programme, 2012). A cervical histology EQA scheme should be introduced to ensure a consistent approach across the programme and all practitioners that are reporting are operating at a minimum quality standard. Even though I have said that Histopathologists only have fair agreement, the cases would need to be carefully selected based on consensus reporting prior to distribution. This would provide confidence to the NHSCSP and the public about reporting standards for cervical biopsies and LLETZ as part of the programme. There have been discussions about the possibility of introducing such a scheme for histology samples reported in the NHSCSP but there has been a reluctance to move this forward. This is because Gynae Histopathologists already take part in a gynaecological pathology EQA which covers all sorts of

specimens as well as LLETZ and cervical biopsies. The introduction a NHSCSP EQA scheme for cervical biopsies and LLETZ should be introduced to monitor standards of reporting and would complement the introduction of Consultant BMS reporting.

Cost Benefits

The Royal College has produced guidelines for staffing histopathology laboratories and we are waiting for the updated version five (Royal College of Pathology, 2015). The document provides guidance to ensure that there are safe and appropriate staffing levels of Histopathologists to cover workloads and to help with job planning. The document uses a point system and points are awarded for all aspects of the Histopathologists' workloads including time for dissection, microscopy reporting and supervision of trainee pathologists and/or BMS.

Medical consultants have job plans and these are split into four hour sessions known as programmed activities (PAs). There are four types of PAs – direct clinical care (DCC), supporting professional activities (SPA), additional NHS responsibilities and external duties. To work out staffing levels based on workloads, points are awarded to the time taken for the specimens ranging from 1 point for 1 to 5 minutes up to 12 points for cases over 50 minutes.

In the RCPath document a LLETZ specimen attracts 3 points and one PA of direct clinical care (DCC) equates to 36 points

per four hour session. In this document is states that time should be allowed for other commitments such as enquiries, extra tests such as immunocytochemistry and supplementary reports associated with more complex cases. If we allow 30 points for direct reporting, a Histopathologist should be able to report 10 LLETZ cases per PA. Taking the midpoint of the medical consultant's pay scale, the annual cost for a NHS Trust is £11,900 per PA. This equates to each PA costing £230 and therefore the cost of reporting each LLETZ specimen is approximately £23.

Looking at mid-point of the Agenda for Change pay scale for 8c which is the grade most Consultant BMS are appointed to, the salary is £64,670. The equivalent cost of a PA for a BMS on 8c would be £132. This means that the costs of a Consultant BMS reporting a LLETZ specimen would be £13.20 which is 43% cheaper than a Histopathologist.

Future Developments

Currently all cervical specimens deemed as part of the NHS cervical screening programme are assessed down the microscope with glass slides. As technology has developed, digital pathology has come to the forefront where the traditional glass slides are scanned to generate a digital image that can be stored electronically and viewed on a high resolution monitor known as the virtual microscope. This allows images to be shared electronically with colleagues anywhere in the world and will be able to help with backlog

reporting Digital marks can be left on the images to get a second opinion from any experts worldwide instantaneously. External quality assurance schemes will enable slides to be transported electronically rather than be posted without the inherent risk of breakage. Good examples of teaching material can also be captured electronically without having to request extra sections or keeping the original slides. The limitation with these images at the moment in the UK is that they are huge and most NHS internet connections do not have the sufficient speed and width to accommodate them.

I would not support using my method of training Consultant BMS as it is a logistical and expensive procedure moving slides around the country for training plus there is a risk of slides breaking. There is the advantage that all the Consultant BMS are looking at the same slides so they can be assessed against their peers and their training can be controlled. This system of training could be reviewed once digital pathology and the infrastructure to support this is fit for purpose.

Once the Consultant BMS are competent to practice independently and with the support of the NHSCSP, RCPath and IBMS they could provide a valuable resource to help with reporting backlogs of work associated with the cervical screening programme. This would be easier to facilitate once it is acceptable for specimens as part of the NHSCSP to be reported digitally.

The Conjoint Board of the RCPath and IBMS should consider looking at other areas of the Histopathology workload where a module structure could be introduced.

Conclusion

This report provides a 'snap shot' of histology reporting of selected samples in this case LLETZ specimens for appropriately experienced BMS with minimal training. As stated earlier, there is a crisis now facing histopathology departments with the chronic lack of Histopathologists and although there are plans to increase the number of Histopathologists, this is going to take time. Due to the consolidation of cervical screening centres in England, there will be a number of Consultant BMS with extensive microscopy skills who will not be in a position to relocate and these skills will be lost to the service. This study provides an option where suitably experienced Consultant BMS can be 'fast-tracked' through an approved training programme to meet the needs of the service in a more timely fashion and provide a cost-effective solution.

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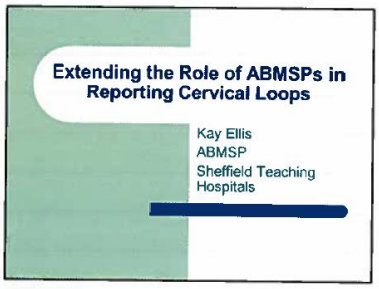
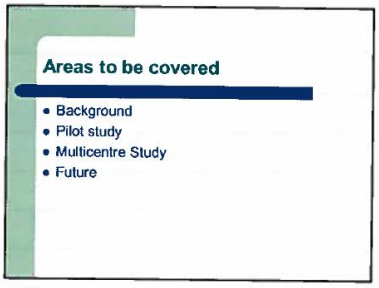
Glossary

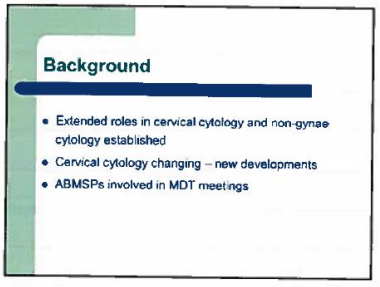
Acronym	Full Wording
ABMSP	Advanced biomedical scientist practitioner
ASD	Advanced specialist diploma
BMS	Biomedical scientist
CIN	Cervical intraepithelial neoplasia
CGIN	Cervical glandular intraepithelial neoplasia
DOH	Department of Health
EQA	External Quality Assurance
FIGO	International Federation of Gynaecology and Obstetrics
GIT	Gastrointestinal tract
HCPC	Health and Care Professionals Council
H&E	Haematoxylin and eosin
HSIL	High grade squamous intraepithelial lesion
HPV	Human Papilloma Virus
HPV PS	HPV primary screening
IBMS	Institute of Biomedical Science
IAC	International Academy of Cytology
LLETZ	Large loop excision of transformation zone
LBC	Liquid based cytology
LSIL	Low grade squamous intraepithelial lesion
MDT	Multi-Disciplinary Team
NHS	National Health Service
NHS CSP	NHS Cervical Screening Programme
NHSE	NHS England
NICE	National Institute for Health and Clinical Excellence
NSC	National screening committee
NBF	Neutral buffered formalin
PHE	Public Health England
QA	Quality Assurance
QC	Quality Control
REC	Research Ethics Committee
RCPath	Royal College of Pathologists
RHH	Royal Hallamshire Hospital
SIL	Squamous intraepithelial lesion
STH FT	Sheffield Reaching Hospitals NHS Foundation Trust

TOC	Test of cure
TBS	The Bethesda System
TATS	Turnaround Times

Appendix A – Presentation







Team

- Dr Branko Perunovic
- Kay Ellis
- Nick Dudding

Pilot Study - Aims

- The aim of the pilot study was to explore the potential for further expansion of the role of ABMSPs in the NHSCSP by reporting the histology of loop excision biopsies of the cervical transformation zone (LLETZ).

Proforma based on Minimum Data Set for Cervical Loops

Wart virus (HPV) infection	Yes/No
CIN	Grade of CIN
CIN present in crypts	Yes/No
Endocervical edge	Yes/No
Deep lateral edge	Yes/No
Endocervical epithelium	Yes/No
Endocervical epithelium at end of canal	Yes / No
Inflammation in cervical stroma	Yes/No
Invasion	Yes/No

2

Pilot Study - Method

- 3 levels per block
- Independently examined by AP1 and AP2
- AP1 and AP2 reports compared to final report
- Reviewed on multi-header
- 104 LLETZ specimens examined
  - 20 (19.2%) no CIN
  - 3 (2.9%) CIN1
  - 14 (13.5%) CIN 2
  - 62 (59.6%) CIN 3
  - 2 (1.9%) CGIN
  - 3 (2.9%) invasive neoplasia

Discussion Points

- 'Real life' reporting vs. study
  - Ways to present findings: proforma vs. free text
  - Simple – yes or no scenarios
  - Committed to a decision – no second opinion

CIN Agreement for ABMSP 1

Histopathologist (CIN)

ABMSP1	0	1	2	3
0	16	1	1	0
1	2	1	1	0
2	1	1	9	3
3	0	0	3	59

Histopathologist (SIL)

ABMSP1	0	L	H
0	8	1	0
L	1	10	2
H	0	3	74

Kappa .742 .812

CIN Agreement for ABMSP 2

Kappa .674 .658

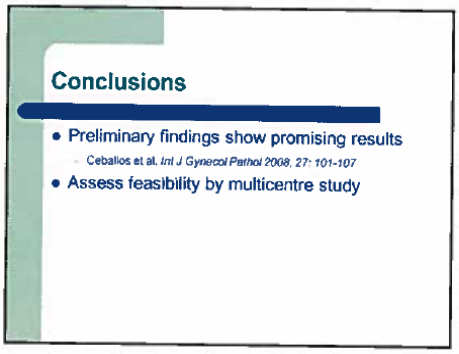
Margins

CIN was present

- 10 (9.6%) endocervical margins
- 12 (11.5%) ectocervical margins
- 1 (1%) deep lateral margins

Perceived difficulties

- Genuine difficult areas
  - Metaplastic vs. CIN
  - Early stromal invasion
  - Interpretation in diathermied tissue
  - CIN in crypts close to margin
  - ...
- Relative inexperience in histology
  - Overemphasis on grade
  - Trying too hard
  - How to examine the specimen
- New concepts for cytologists
  - Margins
  - Visualizing 3-D specimen


Conclusions
• Preliminary findings show promising results
Ceballos et al. Int J Gynecol Pathol 2008; 27: 101-107
• Assess feasibility by multicentre study